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OCTOBER 1953
VOLUME 86 NUMBER 4

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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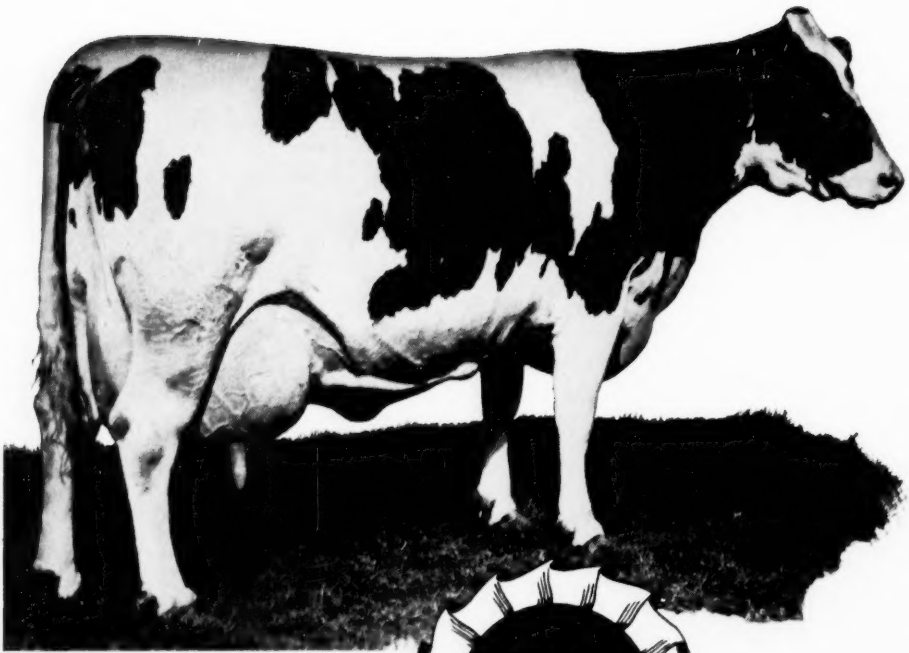

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Communications regarding subscriptions, reprints, etc., should be addressed, A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN, American Medical Association, 535 North Dearborn Street, Chicago 10.

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1. Sebrell, W. H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.

2. Flour and Bread Enrichment, 1949-50: Prepared by The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.

3. Data furnished by the Laboratories of the American Institute of Baking, Chicago, Illinois.

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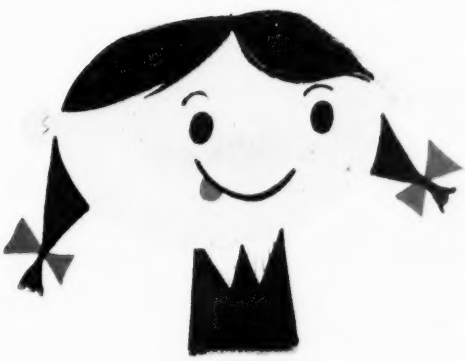

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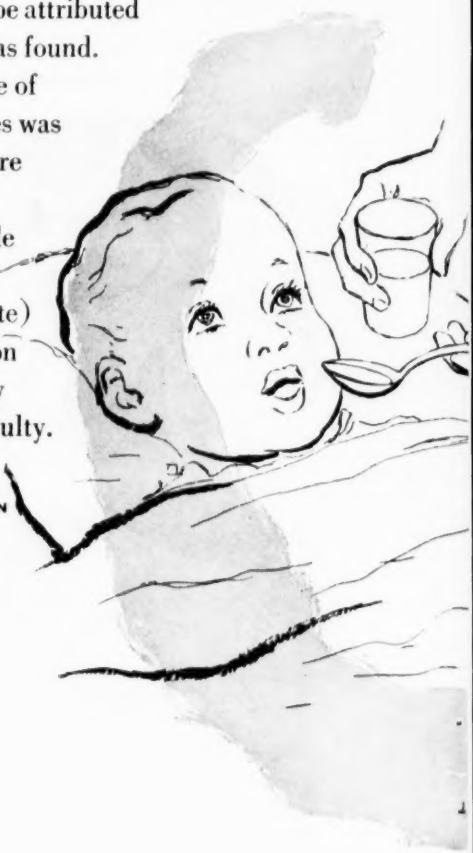

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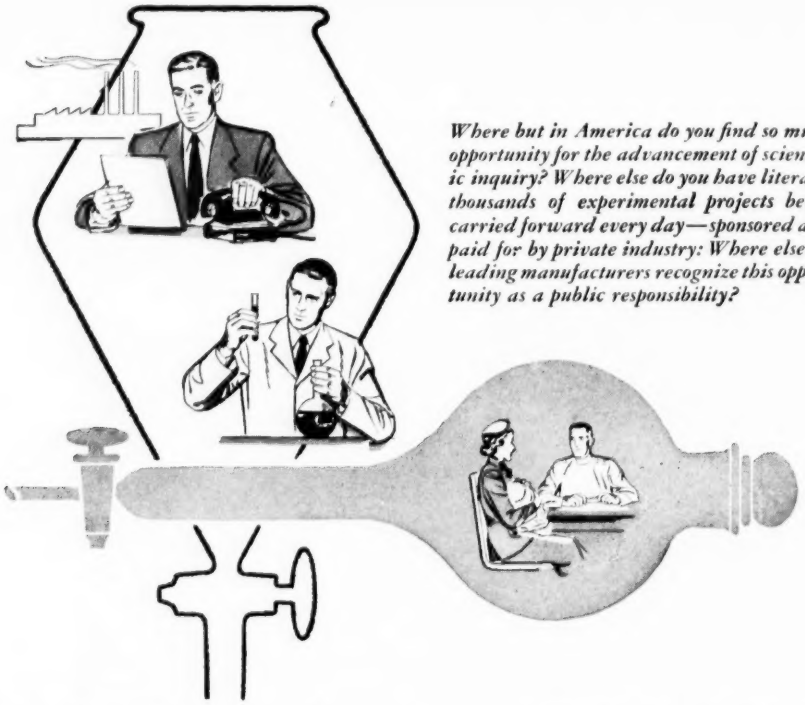

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American Journal of Diseases of Children

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REACTIONS FOLLOWING ANTIRABIES PROPHYLAXIS

Report on Sixteen Patients

NORMAN H. BLATT, M.D.
AND
MARK H. LEPPER, M.D.
With Cooperation of Herman N. Bundesen, M.D.
CHICAGO

NEUROPARALYTIC accidents occurring as a result of administration of rabies vaccine constitute a real problem in the prophylactic program against rabies. These reactions range in severity from minimal transient disability to those producing death. Since the cause is still not well understood and specific treatment is lacking, further study of the problem was felt justified. In this paper data on 16 patients who had untoward reactions to rabies inoculation are reported. In addition, three patients were treated with corticotropin (ACTH), and data on these are reported in detail, since the results seemed promising enough to recommend further trial.

METHOD OF STUDY

Prophylactic Treatment for Rabies.—The patients in the cases reported in this paper were among those who received antirabies inoculations during the years 1950 to 1952 according to the following program:

1. Treatment was started immediately on those bitten anywhere about the person by a stray animal, most frequently a dog, which could not be located for observation.

2. Treatment was started immediately on those bitten about the face and neck, whether the animal was available for observation or not.

3. Treatment was not started immediately on those bitten below the neck when the animal was available for observation. If the animal proved to be rabid during observation, therapy was instituted. If the animal remained well for 14 days, no vaccine was given.

All of the patients received a rabies vaccine prepared by ultraviolet irradiation of rabbit brain containing rabies virus.

Adults, adolescents, and juveniles over 4 years of age, if bitten on the neck or head, received 4 cc. daily for 7 days followed by 2 cc. daily for 7 days, or, if bitten on the trunk or extremities, received 2 cc. daily for 14 days.

Infants and juveniles under 4 years of age, if bitten on the neck or head, received 2 cc. daily for 7 days and then 1 cc. daily for 7 days, or, if bitten on the trunk or extremities, received 1 cc. daily for 14 days.

The vaccine was injected subcutaneously or intramuscularly.

Classification of Reactions.—In this paper we have divided the reactions which developed in patients who received rabies vaccine into two large groups as follows:

I. Transient febrile reaction without signs and symptoms of nervous system involvement

II. Transient febrile reaction with signs and symptoms of nervous system involvement

(*a*) Abnormality of cerebrospinal fluid as only sign

(*b*) Abnormality of cerebrospinal fluid plus signs of meningeal irritation

From the Chicago Board of Health, Municipal Contagious Disease Hospital Section, and the University of Illinois College of Medicine.

TABLE 1.—*Clinical Data on Patients with Reactions to Antirabies Vaccine Who Had No Objective Evidence of Nervous System Involvement*

Patient	Age, Yr.	Race	Sex	No. Vaccine Injections	No. Vaccine Injections After Onset of Symptoms	Length of Fever, Days	Erythema and Induration of Skin at Site of Injection	Skin Tests
V. G.	5/12	N	F	14	1	2	0	..
C. N.	2	W	F	8	2	2	Present	..
J. C.	5	W	M	7	2	2	Present	..
J. H.	6½	W	F	6	0	1	Present	..
A. M.	48	W	M	6	0	2½	0	Positive
H. S.	40	W	M	8	2	1½	Present	Positive
D. K.	5	W	F	10	0	1	Present	..
F. D.	32	W	M	7	0	3½	Present	Positive

TABLE 2.—*Clinical Data on Patients with Reactions to Antirabies*

Patient	Diagnostic Classification*	Age, Yr.	Race	Sex	Site of Bite	No. Vaccine Injections	No. Vaccine Injections After Onset of Symptoms	Day of Onset of 1st Symptom After 14th Injection	Length of Fever in Days	Erythema and Induration of Skin at Site of Injection	Skin Test
J. L.	IIa	12	N	M	L. leg	7	3	..	6	0	Positive
A. S.	IIb	6	W	M	.....	7	1	..	4	0	....
R. P.	IIc	29	W	F	.....	14	0	1	4	Present	....
J. P.	IIc	11	N	M	R. finger	8	1	..	7	0	Positive
L. A.	IIc	30	W	M	Nose	12	4	..	1	Present	Positive
B. B.	IIc	6	W	F	.....	14	0	3	2	Present	Positive
L. K.	IId	8	W	M	Lip	8	1	..	7	0	0
J. P.†	IId	40	W	M	.....	8	0	..	9	0	0

* For criteria see text.
† Patient died after transfer to another hospital.

(*c*) Abnormality of cerebrospinal fluid plus myelitic involvement, commonly known as the dorsolumbar type with or without signs of meningeal irritation

(*d*) Abnormality of cerebrospinal fluid plus signs of encephalomyelitic involvement, commonly known as Landry's ascending paralysis type, with or without signs of meningeal irritation

Another subgroup under II, a neuritic type often characterized by facial paralysis, was not seen among our patients.

Skin Tests.—In an attempt to correlate the appearance of reactions to the rabies vaccine and cutaneous sensitivity to the vaccine, an intradermal skin test was devised. One-tenth of one milliliter of a solution of vaccine diluted 1:10 with 0.85% saline was injected intradermally into the skin of the forearm, and the area was examined 24 hours later. If erythema or induration greater than 1 cm. in diameter was present, the test was interpreted as positive. If there was no reaction or the erythema and induration was less than 1 cm., the test was interpreted as negative.

RESULTS

In 1950, 1951, and the first three months of 1952, the Chicago Health Department gave multiple injections of rabies vaccine to a total of 2,193 persons. Complications developed in 15 of the 2,193 people which were severe enough to cause

referral for diagnosis and treatment. This was a ratio of 1:146 or 0.7%. Of the 15 in whom complications developed, 7 had signs and symptoms of nervous system involvement, a ratio of 1:313, or 0.3%. In addition, one patient (B. B.) received antirabies vaccine inoculation from a private physician and was not included in the Health Department figures. Abnormal neurologic signs developed in this patient.

Pertinent data concerning the patients who had reactions were tabulated in Tables 1 and 2 in the order of increasing severity of symptoms and signs. The first eight patients (Table 1) did not have abnormal neurologic signs, whereas the second eight patients had evidence of brain, spinal cord, or meningeal involvement as indicated in Table 2. Symptomatology has been recorded in Table 3. The most consistent symptom was fever, which was present in all patients. In 10 patients it was the presenting symptom. Other initial symptoms were radicular pain in two

Vaccine Who Had Evidence of Nervous System Involvement

Signs and Symptoms of Nervous System Involvement	Neurologic Residuals on Discharge	Cerebrospinal Fluid: Cell Count: Total Cu. Mm.	Cerebrospinal Fluid: Cell Count: % Lymphocytes	Cerebrospinal Fluid: Protein, Mg. 100 Ml.	Cerebrospinal Fluid: Dextrose, Mg. 100 Ml.	Doses of Cortieotropin
0	0	72	..	37	..	0
Meningeal signs	0	80	100	175	90	0
Positive Babinski	0	60	100	104	70	0
Meningeal signs, weakness of legs	0	80	8	34	68	0
Paralyzed legs; dysuria, sensory changes	Paresthesia, 2 toes	18	96	87	74	50 mg. q6h × 12 days 25 mg. q12h × 4 days
Meningeal signs, leg weakness, sensory changes	Minimal weakness of legs, sensory changes	1,120	70	130	72	20 mg. q8h × 13 days
Meningeal signs, paralysis of legs, weak arms, dysuria, sensory changes	Paralyzed legs, weak arms and trunk, sensory changes	15	..	110	73	20 mg. q8h × 6 days 20 mg. q12h × 5 days 30 mg. q8h × 5 days
Paralysis of legs, weak arms, sensory changes	Weak arms, paralyzed legs, sensory changes	20	100	67	52	0

TABLE 3.—*Symptomatology of Patients with Reactions Following Antirabies Vaccine*

Classification Group	Total Patients	No. Patients Exhibiting Each Reaction: Fever	Weakness of Legs	Headache	Radicular Pain	Local Inflammation	Malaise	Generalized Weakness	Stiff Neck	Faintness or Dizziness	Anorexia	Emesis	Abdominal Pain
I.....	8	8	1	1	2	3	0	1	1	0	1	0	0
II.....	8	8	5	3	3	1	3	1	0	2	0	1	1
Total.....	16	16*	6	4†	5‡	4†	3†	2	1	2	1	1	1

* Presenting symptom in 10.
† Presenting symptom in 1.
‡ Presenting symptom in 3.

patients, local erythema and induration in two, malaise in one, and headache followed by generalized weakness in one. It is interesting to note that three patients had subjective but no objective signs of central nervous system involvement, namely, "generalized weakness, stiff neck, and weakness in the legs."

Four patients without objective nervous system signs received injections of vaccine after the first symptoms of the untoward reaction occurred. Among the eight patients with such signs, five received injections of vaccine after the first symptoms of the complication appeared.

Of the eight patients without objective nervous system signs, erythema and induration developed in six at the site of injection of the vaccine, whereas only three patients out of eight with neurologic involvement are recorded as showing erythema and induration at the site of injection.

All seven patients who were skin tested with antirabies vaccine had positive readings as defined above. Four of these patients had local inflammation at the site of the injection, and three did not.

Among a group of 45 patients who received vaccine therapy and who were skin tested between the 10th and 14th days of injection, 27 had a positive skin reaction (60%); 15 had a negative skin reaction (33%), and 3 had an equivocal reaction (7%). None of these 45 patients had any systemic sensitivity reactions. In addition, 39 patients suffering from other conditions but who had never received antirabies inoculations were skin tested, all with negative or equivocal results.

The patients with evidence of neurologic involvement became ill after the 4th to the 14th injection of rabies vaccine. The cell count in the cerebrospinal fluid ranged from 15 to 1,120 per milliliter. In all instances except one there was a predominance of lymphocytes on the first lumbar puncture. In this one patient the predominance of polymorphonuclear cells present on the first lumbar puncture subsequently was replaced by a predominance of lymphocytes. In all patients the spinal fluid glucose concentration was normal. In all except two patients the spinal fluid protein was elevated above normal and ranged on the first lumbar puncture from 33.6 to 175 mg. per 100 cc.

While the fever in patients without manifest nervous system complications continued from one to three and one-half days, in those with such complications the fever continued from one to nine days, and all but two had fever longer than three and one-half days. The length of fever apparently does not correlate completely with the severity of the disease, even though the three patients with the longest febrile period had severe nervous system involvement.

The more severe the symptomatology on admission, the more apt are neurologic sequelae to persist. Thus among six patients with motor, sensory and/or reflex signs only the two with minimal involvement escaped without residuals.

Since up to this time no therapy had been of much help in management of these patients and since it was felt that adrenal steroids, because of their anti-inflammatory activity, might be of some benefit, corticotropin therapy was tried. The following are the case histories of the three patients who received this.

CASE 1.—L. A. was a 30-year-old married white man who was admitted to the Municipal Contagious Disease Hospital with a chief complaint of "numbness from the waist down." Fourteen days before admission he was bitten on the nose by a dog. On the same day he received his first injection of rabies vaccine. He received an injection thereafter daily for 13 days except for an omission on the eighth day after the first injection because of a temperature of 103 F. On the day of admission, weakness of both legs was noted as well as numbness from the waist down.

Physical examination on admission revealed a cooperative, oriented, well-developed, and well-nourished 30-year-old white man with a temperature of 98.6 F. Questionable weakness of the left leg, hyperesthesia present from the level of the umbilicus to the feet, hyperactive knee reflexes, and erythema and induration of the skin of the buttocks were present.

Laboratory studies revealed a white blood cell count of 7,000, with 58% neutrophiles, 41% lymphocytes, and 1% eosinophiles. Cerebrospinal fluid examination revealed a cell count of 18 per cubic milliliter, with 96% lymphocytes and 4% neutrophiles. The glucose was 74 mg. per 100 cc. and the protein 87 mg. per 100 cc.

Rabies vaccine diluted 1:10 and injected intradermally revealed in 24 hours an area of erythema and induration 1.2 cm. by 1.0 cm.

On the second hospital day dysuria developed, and catheterization was initiated. Also marked weakness of both legs with anesthesia below the level enervated by the first lumbar segment of the spinal cord was noted. On this day, corticotropin treatment, 50 mg. every six hours administered intramuscularly, was instituted and continued for 12 days. By the third hospital day the legs were completely paralyzed. The other findings remained essentially the same. Thereafter there was no progression, and there was a steady improvement of function in the extremities so that by the seventh hospital day the patient was able to lift his legs against gravity. Some dysuria and anesthesia were still present. On the 14th hospital day, corticotropin therapy was discontinued because of hypertension and acne. By the 15th hospital day the patient was up and about walking, but paresthesias of the feet persisted. On the 19th hospital day cystitis and pyelonephritis developed, presumably from the prior catheterization during the early hospital course. These were treated successfully with 1 gm. of sulfisoxazole (Gantrisin) every four hours for five days. Because anesthesia of the little toes of each foot persisted, he received corticotropin again, 25 mg. every 12 hours administered intramuscularly, for another five days, but no further improvement occurred.

He was discharged on the 35th day with persistent paresthesias of both little toes.

Case 2.—B. B. was a 6-year-old white girl who was admitted with a complaint of weakness in both legs.

Nineteen days before admission she received her first antirabies vaccine injection because of a bite by a stray dog. She received thereafter one injection daily for 14 days. Three days after her last injection and two days before admission, fever and malaise developed, for which she received penicillin. On the day of admission weakness of both legs developed.

Past history was nonrelevant. Physical examination on admission revealed a well-developed and well-nourished girl, who was alert but acutely ill. The temperature was 99 F. Nuchal rigidity was present. Both legs were weak. The weakness was symmetrical and diffuse. All deep tendon reflexes were intact. A positive Babinski sign was present bilaterally. Below the level of the sixth thoracic nerve the patient had diminished appreciation to pinprick. There was erythema and induration of both buttocks. Rabies vaccine diluted 1:10 and injected intradermally revealed in 24 hours erythema and induration greater than 1 cm.

Laboratory data on admission revealed a white blood cell count of 13,750, with 63% polymorphonuclear cells, 35% lymphocytes, and 2% eosinophiles. Hemoglobin was 11.0 gm. per 100 ml. The cerebrospinal fluid on admission revealed a cell count of 1,120, with 30% polymorphonuclear cells and 70% lymphocytes. The glucose was 72 mg. per 100 cc., and the protein was 130 mg. per 100 cc. Fourteen days later the cell count was 20 and the protein 28 mg. per 100 cc. During her second hospital day she was started on corticotropin therapy, 20 mg. every eight hours administered intramuscularly. This was continued for 13 days.

On her third hospital day she began to show some improvement in muscular control and strength of her legs. By the eighth hospital day there was further increase in the muscular control of her legs and the ability to appreciate pinprick below the level that had been anesthetic was improving. By discharge on the 19th hospital day, only minimal weakness of both legs persisted, and the sensory changes had almost returned to normal.

Case 3.—L. K., an 8-year-old white boy, was bitten on the lip by a dog 12 days before admission to the hospital. Eight days before admission he began antirabies vaccine therapy and received an injection daily for 8 days, receiving his last injection the day prior to admission even though fever was present. This was followed by emesis and pain in the legs. The following day paralysis and pain in both legs was present, and he was admitted to the hospital. The patient had previously received a complete course of antirabies inoculation at the age of 2 years following a dog bite.

Physical examination on admission revealed a temperature of 104.4 F., respiration 48, and pulse rate 120, in a well-developed, well-nourished white boy. The patient was acutely ill with respiratory distress, nuchal rigidity, positive Kernig sign, absent abdominal, knee and ankle

reflexes, weakness of the intercostal abdominal and back muscles, paralysis of both legs, anesthesia below the level of the ninth thoracic nerve, and dysuria. A lumbar puncture done four days after admission revealed a cell count of 15, glucose 73 mg. per 100 cc., and protein 110 mg. per 100 cc.

On admission, because of respiratory distress, he was placed in a tank respirator in which he remained for 13 days. The paralysis slowly rose to higher cord levels and by seven days after admission there was flaccid paralysis of the arms and the sensory loss extended up to the level of the third thoracic nerve. The cranial nerves remained intact. The patient was afebrile by the sixth hospital day. After this time the paralysis slowly receded so that by the time of discharge, two months after admission, the patient had almost normal function of the arms, weakness of the back and abdominal muscles, spastic paralysis of the legs, a cord bladder, inability to appreciate pinprick, and anhidrosis below the level of the 10th thoracic nerve.

Because of the urinary tract infection with fever starting nine days after admission, the patient received 1 gm. of sulfisoxazole every four hours, at first therapeutically and later prophylactically, for 49 days. He received intramuscularly administered corticotropin, 20 mg.[1] every eight hours beginning on the ninth hospital day for six days, 20 mg. every twelve hours for five days beginning five days later and 30 mg. every eight hours two weeks later for five days.[2] It is difficult to evaluate the part that corticotropin played in the patient's partial improvement, if it played any part at all.

COMMENT

The value of antirabies vaccine in the prevention of rabies has been subject to question. However, in the 1949 to 1950 report of the Pasteur Institute of Southern India, Coonoor,[3] where the Semple vaccine is used, the following statistics were reported:

Total number observed	987
Treated	898
Deaths among treated	8 (0.9%)
Untreated or incompletely treated	89
Deaths among untreated or incompletely treated	28 (31.4%)

The following statistics[4] were reported when the infectivity of the biting animal had been proved by rabies occurring in one of the bitten persons, or in the animal:

Number of persons bitten	146
Number of completely treated persons	84
Deaths from rabies among completely treated	8 (9.5%)
Number of untreated, incompletely treated, and those who died during treatment	62
Deaths from rabies among untreated, incompletely treated, and those who died during treatment	28 (45%)

These statistics are evidence that vaccine should be given when indicated, as it would appear that the treatment given by the Pasteur Institute, Coonoor, saves two out of every three persons who would otherwise have acquired rabies and died.

The exact cause of the reactions which occur from antirabies vaccine has not been definitely established. Several theories[5] have been advanced. Of these, one

1. Adrenocorticotropic hormone (ACTH) used in this patient was about 50% as potent on a weight basis as that used later in the studies.

2. Irregularities in administration were caused by difficulty in procuring the drug, which was not commercially available.

3. Annual Report of the Director 1949-1950, together with the Forty-Third Annual Report of the Central Committee of the Pasteur Institute Association, the Pasteur Institute of Southern India, Coonoor, Madras, Diocesan Press, 1951, p. 16.

4. Footnote 3, p. 15.

5. Van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, New York, Thos. Nelson & Sons, 1948, pp. 876-887.

stands out as the most probable because of the experimental evidence associated with it. This theory [6] states that a constituent of normal nervous tissue is the cause of the neuroparalytic accident. The mode of action of this normal constituent of nervous tissue present in the vaccine upon the nervous system of the patient receiving the vaccine is as yet unknown.

Injections of normal homologous or heterologous brain tissue into rabbits resulted in the animals presenting untoward symptoms.[6] Some rabbits died in convulsions after four to five injections, and paralysis developed in others.

Kabat, Wolf, and Bezer [7] inoculated healthy young Macacus rhesus monkeys with phenolized emulsions of adult rabbit and monkey brain to which Freund adjuvants (paraffin oil and dried tubercle bacilli) were added. Three injections were given intramuscularly at weekly intervals. Ataxia, monoplegia, quadriplegia, ocular paralysis, or tremors usually occurred in the monkeys after about three to four weeks. This symptomatology could not be reproduced when rabbit-lung tissue or fetal rabbit brain free of myelin plus the paraffin oil and dried tubercle bacilli were given.

Wakesman and Morrison [8] have shown that the mechanism of action of the normal constituent of homologous nervous tissue is a tuberculin type sensitivity directed at one or more elements of the nervous tissue of the rabbit (the experimental animal). They demonstrated in experimental isoallergic encephalomyelitis that intracutaneous tests with homologous spinal cord suspended in saline gave reactions having the gross and histologic characteristics of the tuberculin response. This skin reactivity could not be passively transferred with large amounts of serum. In addition, the development of skin reactivity was correlated with the development of experimental encephalomyelitis, both in degree and in time.

Two other investigators, Olitsky and Tal,[9] have shown that the proteolipids A and B of Folch and Lees (normal constituents of bovine brain tissue) plus Freund adjuvants are capable of bringing about in mice acute disseminated encephalomyelitis indistinguishable from that induced by inoculation of whole brain tissue. Proteolipids A and B of Folch and Lees contain practically all of the encephalitogenic agent present in brain. These proteolipids A and B plus Freund adjuvants, when injected intradermally, showed a weakly positive skin reaction in rabbits having experimental encephalomyelitis induced by injection of homologous spinal cord tissue. These positive skin reactions were also shown to be of a tuberculin type.[8]

The intradermal skin test was studied in an attempt to see if there is a correlation between skin sensitivity and reaction to the vaccine. All patients among the seven treated who had a clinical reaction to rabies vaccine were found to have a positive skin reaction. Among 45 people who were skin-tested on the 10th to 14th day of treatment with vaccine and also had no clinical reaction, 60% had a positive skin test. On the other hand, 39 patients who had never received rabies vaccine

6. Van Rooyen and Rhodes,[5] p. 884.

7. Kabat, E. A.; Wolf, A., and Bezer, A. E.: Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Brain Tissue with Adjuvants, Science **104**:362, 1946; The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous and Homologous Brain Tissue with Adjuvants, J. Exper. Med. **85**:117, 1947.

8. Wakesman, B. H., and Morrison, L. R.: Tuberculin Type Sensitivity to Spinal Cord Antigen in Rabbits with Isoallergic Encephalomyelitis, J. Immunol. **66**:421, 1951.

9. Olitsky, P. K., and Tal, C.: Acute Disseminated Encephalomyelitis Produced in Mice by Brain Proteolipide (Folch-Lees), Proc. Soc. Exper. Biol. & Med. **79**:50, 1952.

had no reaction to the skin test. It can be concluded, therefore, that skin sensitivity occurs in a large percentage of persons vaccinated and that only a small percentage of these have systemic symptomatology. However, all patients with vaccine reaction to date have exhibited skin sensitivity. In addition to the skin sensitivity, four of the patients had extensive erythema and induration of the buttocks. This, too, may have been an indication of sensitivity. However, because of the large number of patients with positive skin tests and/or induration and erythema of the buttocks without fever or symptoms of neurological reaction, these findings are not at present a contraindication to receiving further vaccine.

Since corticotropin had been shown to have anti-inflammatory activity in many situations, including experimental encephalomyelitis, it was felt that it should be tried in rabies inoculation reactions. Among the three patients treated with corticotropin, two made rather surprising and rapid improvement and were left with minimal residue. The third patient received small doses of corticotropin quite irregularly and late in the disease and derived no definite benefit.

On the other hand, of the five patients who did not receive corticotropin, one died. The other four had such minimal signs and symptoms it was felt that the drug was not indicated.

Because of the variability of the course of this condition one cannot be sure of the effectiveness of the hormone from the study of several patients, and further evaluation of its usefulness is indicated to see whether there is definite merit.

Even though four patients who had reactions without neurologic signs received one or two doses of vaccine after the onset of symptoms, five others did have progression when further therapy was given. For this reason we feel that vaccine should be stopped immediately upon the appearance of the following symptoms that are otherwise unexplained: fever, headache, emesis, anorexia, radicular pain, generalized weakness, and weakness of the legs.

SUMMARY

In this paper, 16 patients with a reaction to antirabies vaccine are presented. Eight patients showed a reaction without central nervous system signs, and eight patients showed a reaction with such signs, one of whom died and three of whom had neurologic residuals on discharge. All but one of these reactions occurred among 2,193 persons receiving antirabies inoculations.

The signs and symptoms of antirabies-vaccine reaction which indicate that therapy should be discontinued are presented. Occurrences of an otherwise unexplained fever, paresis, radicular pain or headache are most important, but any complaint not obviously due to another disease must be considered potentially dangerous.

An intradermal skin test, using antirabies vaccine diluted 1 : 10, was found to be positive in all patients in whom a clinical reaction to rabies vaccine developed. However, 60% of all persons being vaccinated showed positive tests. On the other hand, persons who have not been inoculated with rabies vaccine have negative skin tests.

Corticotropin was given to three of the patients with the most serious involvement. Two responded well and the third, who received the drug late in the course of the disease, had only questionable benefit. It was suggestive but not proved that corticotropin may have been effective in treating these patients who were suffering from reactions to antirabies inoculations.

ELECTROPHORETIC ANALYSES OF PLASMA OR SERUM PROTEINS OF RHEUMATIC-FEVER PATIENTS IN RELATION TO STAGES OF DISEASE

ROBERT L. JACKSON, M.D.
HELEN G. KELLY, M.S.
ELIZABETH KNAPP SMITH, Ph.D.
PAULINE WANG, M.D.
AND
JOSEPH I. ROUTH, Ph.D.
IOWA CITY

THE REASONS certain children have rheumatic fever and why clinical manifestations and course of the disease vary so widely in children and adults who have the disease are unknown. Evidence has increased rapidly to indicate that Group A hemolytic streptococci, or the soluble antigens produced by them, precipitate the onset of the disease.[1] The part host factors play in the course of rheumatic fever is not clearly understood. Variation in the incidence and manifestation of the disease at different age levels indicate certain host differences. During mid-childhood the incidence of rheumatic fever is at a maximum and is characterized by carditis. Although rheumatic fever is found rarely in children under 4 years of age, its occurrence is accompanied generally by a more severe carditis. The incidence of clinically recognizable rheumatic fever is highest in children living in adverse environmental situations, but what and how factors associated with poor living conditions influence the disease is not clearly understood.

Aided by Grants from Hoffmann-LaRoche, Inc., and the Iowa Heart Association.

From the Departments of Pediatrics and Biochemistry, State University of Iowa College of Medicine, and State Services for Crippled Children.

1. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931. Jones, T. D., and Mote, J. R.: The Clinical Importance of Infection of the Respiratory Tract in Rheumatic Fever, J. A. M. A. **113**:898, 1939. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, Bulletin, New York Metropolitan Life Insurance Company, 1943. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131, 1945. Kuttner, A. G., and Reyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, J. Clin. Invest. **22**:77, 1943. Swift, H. F.: The Etiology of Rheumatic Fever, Ann. Int. Med. **31**:715, 1949. Murphy, G. E., and Swift, H. F.: Induction of Cardiac Lesions, Closely Resembling Those of Rheumatic Fever, in Rabbits Following Repeated Skin Infections with Group A Streptococci, J. Exper. Med. **89**:687, 1949. Rothbard, S.; Watson, R. F.; Swift, H. F., and Wilson, A. T.: Bacteriologic and Immunologic Studies on Patients with Hemolytic Streptococcic Infections as Related to Rheumatic Fever, Arch. Int. Med. **82**:229, 1948.

In the adjustment of the child to acute disease a number of changes occur in the serum-protein components of the blood in addition to the antibody response. There may be characteristic changes in the protein components depending on the tissue reactions of the host to the same noxious agent, and these in turn may be dependent on the nutritional and immunological status of the child.

In this clinic detailed information is obtained for each child observed with definite rheumatic fever to evaluate the child's preclinical condition, especially the nutritional status, the severity and management of the antecedent infection, and the adequacy and promptness of treatment of the disease. Children with rheumatic fever are observed by our research staff in the hospital and convalescent wards until the disease is considered inactive. Clinical manifestations of the disease, type of treatment, and laboratory data are recorded. As the data accumulate, we plan to determine the intercorrelation of factors such as the preclinical state of the child, the nutritional status, the severity of the antecedent infection and the clinical manifestations, the type and duration of the disease, and alterations in the composition of the plasma or serum proteins.

We have decided as a first step to report our data on the alterations in the percentage composition of the serum- or plasma-protein components in relation to the course of the disease, as a definite pattern was found which may provide a baseline for future studies. Although electrophoretic analyses of plasma or serum proteins have been reported for groups of rheumatic fever patients,[2] both adults and children, we are aware of no report of a large series of such analyses studied in relation to the clinical status of the patient.

Dole, Watson, and Rothbard [2a] studied the changes in the electrophoretic pattern of six patients originally admitted with scarlet fever, in three of whom rheumatic fever subsequently developed. From their series they concluded that there were no changes in the serum-protein pattern, detectable by the method used, to distinguish rheumatic from nonrheumatic patients. The greater duration of abnormalities in the rheumatics was assumed to be a reflection of the physiological disturbances associated with continued rheumatic activity. They state that the serum-protein changes in the nonrheumatic patients presumably reflected a host reaction to infection with hemolytic streptococci. In the rheumatic subjects, although the original changes can be explained equally well by the same host reaction the reason for the greater delay in return to normal is not evident. In view of the nonspecific nature of the observed serum-protein changes, it can only be said that the protracted changes reflected the physiological disturbances associated with continued rheumatic inflammation. Wilson and Lubschez,[3] in a study of 79 specimens of plasma or serum from 42 subjects in various stages of rheumatic fever, found a normal gamma-globulin concentration during the acute stage, if there

2. (a) Dole, V. P.; Watson, R. F., and Rothbard, S.: Electrophoretic Changes in the Serum Protein Patterns of Patients with Scarlet Fever and Rheumatic Fever, J. Clin. Invest. **24**:648, 1945. (*b*) Wilson, M. G., and Lubschez, R.: Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever: Electrophoretic Patterns of Blood Plasma and Serum in Rheumatic Children, Pediatrics **2**:577, 1948. (*c*) Lubschez, R.: Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever: Electrophoretic Patterns in Blood Plasma and Serum in Normal Children, ibid. **2**:570, 1948.

3. Wilson and Lubschez.[2b] Lubschez.[2c]

was no history of an antecedent illness. Elevation of the gamma-globulin component in rheumatic fever was considered not to be a function of the rheumatic process. In their patients, the alpha-globulin components were elevated usually during febrile periods. They found no evidence in their studies that the immune response of rheumatic subjects to infections, presumably streptococcal in origin, differed from that of nonrheumatic subjects.

MATERIALS AND METHODS

This report is based on the electrophoretic analyses of the proteins of 205 plasma or serum samples from 77 children with definite rheumatic fever treated by standard nonspecific methods of therapy and 5 patients with chorea without other manifestations of rheumatic fever. The specimens were obtained during hospitalization and at follow-up visits in the outpatient clinic of the Children's Hospital, State University of Iowa. In our earlier studies plasma was used, but more recently only serum has been used.

During the active phase of the disease the patients were observed by the research staff, and blood was obtained for electrophoretic analysis in the various stages of the disease. Samples of plasma and serum were obtained from either oxalated or untreated blood. The plasma or serum was diluted with 3 vol. of a barbiturate buffer (pH 8.6, ionic strength 0.1) and dialyzed in Visking casings at 2 to 6 C. for three days with daily change of buffer. Electrophoresis was carried out in the Longsworth modification of the Tiselius apparatus with use of the long-center-section analytical cell. The current was maintained at a value of 25 ± 0.5 ma. for 120 ± 1 minute. The patterns were photographed, and projections (2.5 ×) were traced on bond paper. The area enclosed by the baseline and the protein peaks was measured separately to determine values for individual components. Mobility measurements were made from the center of the boundary anomaly of each pattern.

The data are subdivided and analyzed according to the stages of the disease, namely, early acute, late acute, early subacute, midsubacute, late subacute and inactive. The data are divided further into subgroups relative to the presence or absence of decompensation and of an intercurrent infection or exacerbation at the time the specimens were obtained. The subjects with a remittent type of disease and those with active chorea without other manifestations of rheumatic fever are considered in two separate subgroups. The mean and standard deviations of the plasma- and serum-protein components are computed for each subdivision, and the mean values for the various stages of the disease are compared with each other and with the mean values for normal children. For each subgroup an analysis is made and summarized of the pertinent clinical findings, which include temperature, erythrocyte sedimentation rate, presence of organic murmurs, and the length of time since onset. A correlation coefficient for the relationship between each of the protein components and the sedimentation rate is calculated.

FINDINGS IN VARIOUS STAGES OF DISEASE

Patients Observed in the Acute Stage of the Disease.—Thirty electrophoretic analyses of the plasma or serum proteins of 24 patients in the acute stage of the disease were made. Fourteen specimens were obtained during the early- and 16 during the late-acute stage. Nine observations were made on children with cardiac decompensation at the time the blood samples were collected, three in the early- and six in the late-acute stage of the disease. One observation during the early-acute stage was on a child with a remittent type of rheumatic fever.

Early Acute, Without Decompensation.—The data on 10 children in the early-acute stage of the disease without cardiac decompensation are presented in Table 1 and the Chart. For comparison the values for normal children of the same age range [4] as the rheumatic-fever patients are also presented in Table 1 and the Chart.

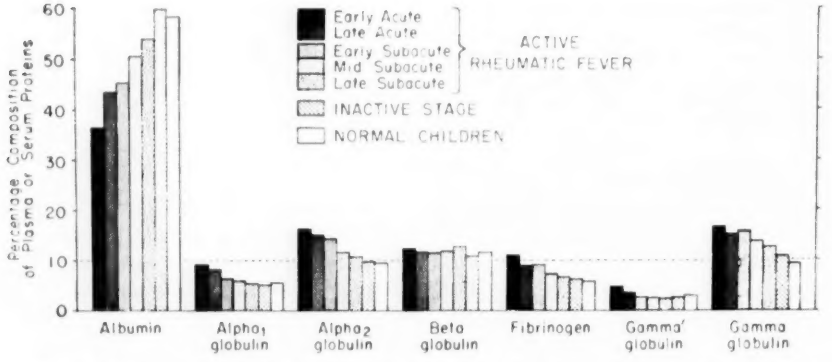
4. Knapp, E. L., and Routh, J. I.: Electrophoretic Studies of Plasma Proteins in Normal Children, Pediatrics **4**:508, 1949.

A specimen was obtained from each of these patients early in the course of the disease, the median length of time from onset being one week. All were experiencing fever and carditis without decompensation. The sedimentation rates range from

TABLE 1.—*Electrophoretic Analysis of Proteins in Plasma or Serum of Rheumatic-Fever Patients in the Early-Acute Stage of the Disease Without Decompensation*

Patient	Age, Yr.-Mo.-Day	Percentage Composition							Total Proteins, Gm./100 Ml.
		Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma' Globulin	Gamma Globulin	
F. Z.	12- 3- 7	38.9	8.6	13.1	14.4	13.2	...	11.8	6.7
G. S.	11-10- 1	37.9	9.5	18.7	10.1	7.4	...	16.4	7.7
P. R.	11- 8-16	45.0	7.0	12.0	11.1	12.6	...	12.3	7.7
L. P.	12- 9-28	32.1	7.8	19.1	11.6	10.3	...	19.1	8.1
H. B.	8- 6-15	39.4	12.2	15.1	11.0	11.3	...	11.0	9.0
D. R.	12- 1-20	26.8	8.1	16.2	12.6	14.3	...	22.0	8.9
L. F.	3-10-18	33.8	11.9	22.9	13.4	....	3.6	14.4	7.9
M. B.	12-10- 9	39.7	8.8	18.1	12.1	....	5.3	16.0	7.1
A. D.	13- 1-14	27.9	10.4	16.8	13.0	....	4.9	27.0	6.9
C. B.	10-11-14	41.4	7.0	11.5	11.5	10.4	...	17.8	5.8
No. patients		10	10	10	10	7	3	10	10
No. observations		10	10	10	10	7	3	10	10
Mean		36.5	9.1	16.2	12.2	11.1	4.6	16.7	7.7
Standard deviation		5.66	1.78	3.41	1.28	2.24	...	4.73	1.0
Clinical summary at time of observation of proteins: 100% with fever; 100% with signs of active carditis; Erythrocyte sedimentation rate range from 57 to 131 mm. in 45 min.—mean 91 mm. (Westergren); Interval from onset range 4 to 18 days—median 1 wk.									
Normals (age 5 to 17 yr.)									
Number		31	31	31	31	31	18	31	31
Mean		58.4	5.7	9.7	11.5	5.4	2.5*	9.3	7.4
Standard deviation		3.56	1.88	1.44	2.94	1.30	...	2.51	.57

* Range between 1.7 and 3.4%.[10a]



The alterations in the plasma or serum proteins of 77 rheumatic-fever patients are depicted in relation to the stages of the disease.

57 to 131 mm. in 45 minutes by the Westergren method and average 91 mm. for the group at the time the specimens were obtained. All 10 values for albumin are definitely out of the normal range, that is, deviated two standard deviations or more from the mean for the normal children. With the exception of beta globulin, which remains consistently within the normal range, the values for all protein

fractions tend to be abnormal. Eighty-six per cent of the fibrinogen values, 40% of alpha$_1$, 80% of alpha$_2$, 100% of gamma′, and 70% of gamma-globulin values are definitely abnormal. The mean values for the percentage composition are albumin 36.5, fibrinogen 11.1, and the globulins, alpha$_1$ 9.1, alpha$_2$ 16.2, beta 12.2, gamma′ 4.6, and gamma 16.7. The mean values of all the protein components except beta globulin for the acutely ill children are significantly different from the normal values. The magnitude of the total protein is not changed from normal. The mean value for gamma′ globulin is based on fewer samples than the other fractions, but the three samples obtained in the acute stage of the disease are outside the range of values for normal children.

TABLE 2.—*Electrophoretic Analysis of Proteins in Plasma or Serum of Rheumatic-Fever Patients in the Late-Acute Stage of the Disease Without Decompensation*

Patient	Age, Yr.-Mo.-Day	Percentage Composition							Total Proteins, Gm./100 Ml.
		Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma′ Globulin	Gamma Globulin	
R. C.	4-11- 5	39.9	9.1	21.4	15.3	5.4	...	8.9	6.0
R. H.	14- 3-24	50.3	6.5	17.5	6.5	....	2.8	16.4	6.9
R. H.	14- 3-26	48.2	8.4	15.6	11.6	....	2.7	13.5	7.1
D. R.	12- 2- 6	44.3	6.0	13.3	15.1	8.2	...	13.1	10.2
M. M.	11- 4-19	33.7	9.1	15.5	12.7	11.0	...	18.0	6.7
R. L.	7- 9- 3	42.9	9.9	12.3	11.6	8.3	...	15.0	8.9
P. R.	11- 8-28	45.4	7.4	15.3	11.8	7.5	...	12.6	7.2
A. D.	13- 2-10	45.6	4.9	13.7	11.5	8.1	...	16.2	8.1
S. B.	11- 1-14	46.2	8.8	9.9	10.6	....	4.4	20.1	8.9
C. K.	13- 2-15	34.2	10.8	15.2	11.5	12.1	...	16.2	8.9
No. patients.....		9	9	9	9	7	3	9	9
No. observations.....		10	10	10	10	7	3	10	10
Mean		43.1	8.1	15.0	11.8	8.7	3.3	15.0	7.9
Standard deviation.....		5.56	1.85	2.94	2.46	2.22	...	3.14	1.35

Clinical summary at time of observation of proteins:
30% with fever
80% with signs of carditis
Erythrocyte sedimentation rate range from 37 to 110 mm. in 45 min.—mean 73 mm. (Westergren)
Interval from onset range 2 wk. to 2.5 mo.—median 24 days.

Late Acute, Without Decompensation.—Ten samples of blood were obtained from nine patients in the late-acute stage of the disease. The data obtained on the children in the late-acute stage are shown in Table 2 and the chart. The interval from onset of the disease to the day the specimen was obtained ranges from two weeks to two and one-half months, the median value for the group being 24 days. Fever was present in 30% of the children on the day the specimen was obtained. Eighty per cent had signs of active carditis without decompensation. The sedimentation rates range from 37 to 110 mm. in 45 minutes, and the mean value is 73 mm. Many of the percentage composition values for the protein components are definitely out of the normal range—100% of the albumin, 71% of the fibrinogen, and of the globulins, 20% of alpha$_1$, 80% of alpha$_2$, none of beta, 33% of gamma′, and 60% of gamma. The mean values of the percentage composition of the components are albumin 43.1, fibrinogen 8.7, and the globulins, alpha$_1$ 8.1, alpha$_2$ 15.0, beta 11.8, gamma′ 3.3, and gamma 15.0. The mean values for all components except beta globulin are significantly different from the corresponding normal values. The mean values for the late-acute stage (with the exception of beta) are less deviant

TABLE 3.—*Means and Standard Deviations of the Electrophoretic Analysis of Proteins in Plasma or Serum of Rheumatic-Fever Patients in Early-, Mid-, and Late-Subacute Stage of the Disease Without Decompensation or Recent Infection or Exacerbation*

	Percentage Composition							Total Proteins, Gm./ 100 Ml.	Clinical Summary at Time of Observation of Proteins
	Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma$'$ Globulin	Gamma Globulin		
Early-Subacute Stage									
No. patients	11	11	11	11	9	3	11	11	21.4% with fever; 100% with signs of active carditis; erythrocyte sedimentation rate range 16-109, mean 53.8; interval from onset range 23 days-3 mo., median 1.8 mo.
No. observations	14	14	14	14	9	5	14	14	
Mean	45.3	6.3	14.5	11.6	8.9	2.4	15.7	7.6	
Standard deviation	5.42	.98	3.85	3.64	3.28	...	2.71	.83	
Midsubacute Stage									
No. patients	28	28	28	28	21	7	28	28	11.4% with fever; 88.6% with signs of carditis; 1 patient with a ? murmur; erythrocyte sedimentation rate range 9-56, mean 27.8; interval from onset range 24 days-12 mo., median 3.3 mo.
No. observations	35	35	35	35	26	9	35	33	
Mean	51.0	6.0	11.5	11.7	7.1	2.4	13.9	7.6	
Standard deviation	4.69	1.62	2.29	2.64	1.21	.90	2.82	.75	
Late-Subacute or Early-Inactive Stage									
No. patients	31	31	31	31	24	6	31	27	5.4% with fever; 81.1% with a residual murmur; erythrocyte sedimentation rate range 2-31, mean 13.7; interval from onset range 6 wk.-20 mo., median 4.2 mo.
No. observations	37	37	37	37	29	8	37	33	
Mean	53.8	5.5	10.6	12.7	6.4	2.2	12.2	7.8	
Standard deviation	3.82	1.09	1.71	2.62	1.51	.39	2.65	.92	

from the normal than the corresponding mean values in the early-acute stage. Forty per cent of the total protein values are definitely out of normal range of values, but the mean value, 7.9 gm. per 100 ml., is not significantly different from the mean for normal children.

Subacute, Without Decompensation.—In the early-subacute stage and the mid-subacute stage the mean values for alpha$_1$ globulin, beta globulin, and total proteins are not significantly different from the normal values, whereas albumin, alpha$_2$ globulin, fibrinogen, and gamma globulin are definitely different (Table 3 and the chart). In the late-subacute stage albumin and gamma globulin are definitely different from the normals; alpha$_2$ globulin, fibrinogen, and total proteins also differ significantly from the normals, but with a less degree of confidence.

The return to normal appears to be more prompt for alpha$_1$ than for alpha$_2$ globulin. Beta globulin does not show much tendency to be altered for the groups as a whole, except to be elevated slightly in the late-subacute stage.

TABLE 4.—*Means and Standard Deviations of the Electrophoretic Analysis of Proteins in Plasma or Serum of Inactive Rheumatic-Fever Subjects Without Recent Infection or Exacerbation*

	Percentage Composition							Total Proteins, Gm./100 Ml.
	Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma' Globulin	Gamma Globulin	
No. patients	23	23	23	23	9	14	23	22
No. observations	26	26	26	26	9	17	26	24
Mean	59.8	5.2	9.8	10.8	6.3	2.3	10.7	7.5
Standard deviation	3.39	1.36	2.02	2.34	1.03	.83	2.63	.85

Clinical summary at time of observation of proteins:
0 with fever
73.1% with a residual murmur
Erythrocyte sedimentation rate range 2 to 19—mean 7.3 mm. in 45 min. (Westergren)

The albumin and gamma globulin exhibit the most marked disturbance and return to normal in a parallel fashion. Alpha$_2$ globulin and fibrinogen are altered markedly and show some paralleling in degree of disturbance and in the rate of return to normal.

The mean values for gamma' globulin in the subacute stage are based on fewer observations than the other components, but do not appear to differ significantly from normal.

Inactive.—The mean values for the percentage composition of electrophoretic protein components for 26 observations made on 23 patients with inactive disease and free from recent intercurrent infection or exacerbation do not differ significantly from the mean values of normal children (Table 4 and the chart). The protein values of inactive patients are presented in subsequent paragraphs in relation to the erythrocyte sedimentation rate and infection.

Acute, with Decompensation.—The three observations in three patients in the early-acute stage with decompensation show alterations similar to the group of children in the same stage without decompensation, with the exception that alpha$_2$-globulin values are more elevated and beta-globulin values tend to be lower for those with cardiac decompensation (Table 5).

TABLE 5.—*Electrophoretic Analysis of Proteins in Plasma or Serum of Rheumatic-Fever Patients in the Acute Stage of the Disease with Decompensation*

Patient	Age, Yr.-Mo.-Day	Percentage Composition: Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma' Globulin	Gamma Globulin	Total Proteins, Gm./100 Ml.	Comments
Early-Acute Stage										
W. A.	10- 4-29	37.2	12.6	17.6	4.0	17.3	...	11.3	7.0	
A. M.	14- 5-10	33.6	11.0	24.1	10.6	8.2	...	12.5	6.2	
G. V. L.*	.....	32.3	9.9	24.1	6.5	8.8	...	18.4	7.3	Died 23 days after observation
No. patients		3	3	3	3	3	...	3	3	
No. observations		3	3	3	3	3	...	3	3	
Mean		34.4	11.2	21.9	7.0	11.4	...	14.1	6.8	
Clinical summary at time of observation of proteins: 100% with fever; 100% with decompensation; Erythrocyte sedimentation rates 102, 122, and 117; Interval from onset range 5 days to 3 wk.										
Late-Acute Stage										
J. F.	10-11-17	43.0	9.5	17.9	8.8	7.6	...	13.2	7.0	
K. H.	7- 2-23	41.9	8.3	12.6	11.2	8.7	...	17.3	7.4	
T. H.	13- 6- 8	34.7	12.5	18.6	16.2	9.9	...	8.1	6.3	
K. S.	15- 7- 4	39.4	7.4	14.4	13.3	10.5	...	15.0	6.8	
K. S.	15- 7-11	50.8	5.0	14.1	9.0	8.4	...	12.7	6.4	.....
K. S.	15- 7-16	48.5	7.2	14.2	9.9	6.3	...	13.9	7.2	
No. patients		4	4	4	4	4	...	4	4	
No. observations		6	6	6	6	6	...	6	6	
Mean		43.0	8.3	15.3	11.4	8.6	...	13.4	6.8	
Standard deviation		5.90	2.53	2.39	2.89	1.54	...	3.06	.58	
Clinical summary at time of observation of proteins: 100% with fever; 100% with decompensation; Erythrocyte sedimentation rate range from 9 to 93 mm. in 45 min.—mean 46 mm. (Westergren); Interval from onset range 6 wk. to 3.5 mo.—median 2.2 mo.										

					Chronic Decompensation					
E. P.	15- 7- 6	50.5	5.5	10.3	13.6	....	...	20.1	8.9	
T. H.	6- 9-29	54.4	5.2	9.6	15.6	5.4	...	9.8	6.2	
M. M.	14- 8- 4	40.7	3.4	11.0	14.1	9.9	...	20.9	...	
M. M.	14-10-25	54.6	4.7	11.5	8.7	6.3	...	14.2	...	
A. M.	14- 8-18	54.2	6.8	9.3	11.9	5.9	...	11.9	7.0	
A. M.	14-10-26	45.1	7.5	12.5	13.7	8.6	...	12.5	9.5	Postexacerbation
G. G.	7- 5- 7	48.8	6.8	9.4	17.3	5.9	...	11.8	6.4	Died 15½ mo. later
G. G.	7-11-11	53.3	6.1	7.3	15.2	4.4	...	13.7	9.0	Died 9½ mo. later
No. patients		5	5	5	5	4	...	5	4	
No. observations		8	8	8	8	7	...	8	6	
Mean		50.2	5.8	10.1	13.8	6.6	...	14.4	7.8	
Standard deviation		5.88	1.36	1.60	2.61	1.94	...	4.02	1.50	

Clinical summary at time of observation of proteins:

0 with fever
100% with chronic decompensation
Erythrocyte sedimentation rate range from 3 to 107 mm. in 45 min.—mean 31.1 mm. (Westergren)
Interval from onset range 7 wk. to 15 mo.—median 7 mo.

					Patients in this Subgroup had Chronic Decompensation with Acute Exacerbation and Subsequently Died					
D. V.	11-..-..	34.3	11.3	20.7	8.3	....	4.7	20.7	6.6	Died 8 days later
G. C.	13-..-..	27.5	11.0	16.9	6.1	8.4	...	30.1	8.3	Died 2 days later
D. S.	8- 1 -1	34.6	8.8	16.8	6.7	10.7	...	22.4	7.7	Died 32 days later
No. patients		3	3	3	3	2	1	3	3	
No. observations		3	3	3	3	2	1	3	3	
Mean		32.1	10.4	18.1	7.0	9.5	4.7	24.4	7.5	

Clinical summary at time of observation of proteins:

100% with fever
100% with chronic decompensation
Erythrocyte sedimentation rates 122, 65, and 58
Intervals from onset are all 6 mo.

* G. V. L. had the fulminating type of disease.

A comparison of the mean values of the plasma proteins for 6 observations on patients in the late acute stage with cardiac decompensation with the mean values of the 10 observations in the same stage without cardiac decompensation, shows the values for the various corresponding components to be similar.

The plasma specimens of the nine patients in this group exhibit a slight lowering in total protein content, the mean value being 6.8 gm. per 100 ml.

Chronic Cardiac Decompensation.—Eight observations of the plasma proteins were made on five patients with chronic cardiac decompensation. The mean value of 50.2% for albumin and 14.4% for gamma globulin show moderate but prolonged alterations, whereas the mean values for the remaining components are normal or only slightly altered.

The one patient in the early-acute stage of the disease with cardiac decompensation and the three children with chronic cardiac decompensation with an acute exacerbation who died the ensuing month after the electrophoretic analyses of the proteins were made, show greatly altered patterns. The mean values of the percentage composition of the proteins for the four observations are albumin 32.5, fibrinogen 9.0, and the globulins, alpha$_1$ 10.3, alpha$_2$ 18.1, beta 8.4, and gamma 22.7.

Recent Intercurrent Infection or Exacerbation and Alterations in the Protein Components of the Blood.—Table 6 shows the mean values of the percentage composition of the plasma- and serum-protein components during the subacute stage of the disease in patients who experienced an intercurrent respiratory infection or had an exacerbation of their disease at the time the specimen was collected. When the protein values for these patients are compared with those in the subacute stage without an intercurrent infection (Table 3), no significant difference in the mean electrophoretic values is noted. Comparing the midsubacute groups, which are the largest groups of patients with an infection, and patients without an intercurrent infection or an exacerbation, none of the mean values of the protein components differs significantly; in fact they are remarkably similar for the two groups. The records show more patients with fever in the midsubacute group with an infection or an exacerbation than in the midsubacute group without a recent infection or exacerbation, 46.2% compared to 11.4%, but the mean and range of the erythrocyte sedimentation rate are almost identical for the two groups.

The blood protein observations in the subacute stages of the disease which were made during or within a month after an intercurrent respiratory infection were analyzed apart from groups in the subacute stage not experiencing infection or exacerbation, because it was thought that the infections might alter significantly the protein components and change the picture we were attempting to obtain during the course of uncomplicated rheumatic fever.[2c] Sixty-one per cent of the observations on patients in the midsubacute stage were made when the patients were improving or had clinically recovered from a recent intercurrent respiratory infection. All patients with a definite pharyngitis were treated immediately with antibiotics. These factors probably account for the slight change in protein pattern noted in this group of patients with recent infection and exacerbation. The patient in the group with the most marked alteration was B. W., in whom a cold with slight fever was developing at the time the blood was obtained for the electro-

TABLE 6.—*Means and Standard Deviations of the Electrophoretic Analysis of Proteins in Plasma or Serum of Rheumatic-Fever Patients in Early-, Mid-, and Late-Subacute Stage of the Disease Without Decompensation but With a Recent Mild Intercurrent Infection or Exacerbation*

	Percentage Composition							Total Proteins, Gm./100 Ml.	Clinical Summary at Time of Observation of Proteins
	Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma' Globulin	Gamma Globulin		
Early-Subacute Stage									
No. patients	2	2	2	2	2	....	2	2	None with fever; all had signs of active carditis; erythrocyte sedimentation rates 30, 42, and 35; interval from onset, 4 mo., 1 mo., and 1.3 mo.
No. observations	3	3	3	3	3	....	3	3	
Mean	46.7	6.9	14.4	9.9	7.8	....	14.3	7.6	
Standard deviation	....	....	....	....	....	....	....	....	
Midsubacute Stage									
No. patients	12	12	12	12	9	3	12	12	46.2% with fever; 77.0% with signs of carditis; 1 patient with a [illegible] murmur; erythrocyte sedimentation rate range from 6 to 60, mean 28.0; interval from onset range, 3 wk.-11 mo., median 4 mo.
No. observations	13	13	13	13	9	4	13	13	
Mean	51.4	6.3	12.2	10.7	7.9	2.4	13.2	7.7	
Standard deviation	6.19	1.68	2.77	2.82	1.98	....	3.11	.83	
Late-Subacute or Early-Inactive Stage									
No. patients	7	7	7	7	5	2	7	7	None with fever; 85.7% with a residual murmur; erythrocyte sedimentation rate range from 5 to 35, mean 13.4; interval from onset range, 1.5 mo.-15 mo., median 5.5 mo.
No. observations	7	7	7	7	5	2	7	7	
Mean	53.9	4.7	10.4	12.2	6.5	3.2	13.2	7.4	
Standard deviation	2.65	1.94	2.02	3.30	1.75	....	2.89	.63	

phoretic pattern. The disease had been in the midsubacute stage fo rtwo months when this cold developed. The protein values in the midsubacute stage two months prior to the cold and those when the cold was developing are as follows:

	Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma Globulin
11/18/46	50.1	5.7	12.6	11.5	6.6	13.5
1/20/47	39.6	6.8	14.8	5.7	12.3	20.8

L. L., a patient with remittent type of disease, had an infection with fever when she was in the subacute stage of her disease. Within the week after this infection her electrophoretic pattern was obtained and found to be more altered than her previous one, which was obtained during the same stage of the disease. The values are as follows:

	Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Gamma' Globulin	Gamma Globulin	E.S.R.
6/ 1/50	54.7	5.4	10.4	13.1	4.2	12.2	23
8/10/50	48.9	10.6	14.9	11.2	3.2	11.2	30

Chorea, Without Other Manifestations of Rheumatic Fever.—The plasma or serum proteins of patients with active chorea without other manifestations of rheumatic fever were studied in five patients. The sedimentation rate for the group ranges from 7 to 12 with a mean of 9.8 mm. in 45 minutes. The mean values for the protein components are given in Table 7. The mean values for the albumin, alpha$_2$ globulin, and gamma globulin are significantly different from the normal values. The difference is more evident in the albumin and alpha$_2$-globulin components.

Remittent Type.—Twenty-two specimens were obtained from patients with a remittent type of rheumatic fever (Table 8). One sample was obtained during the acute stage, 17 during the subacute stage, and 4 during the inactive stage. The data do not show this type of disease to be related to any unusual protein alteration, the values for comparable stages of remittent and monocyclic rheumatic fever being similar. A possible exception is the tendency of the gamma globulin to be higher in the remittent group than in the monocyclic group. Evidence does not indicate that the alteration of any protein component is related to the protracted course of the disease, except that it takes the patients longer to be rehabilitated and to have the protein values return to normal. The mean of four observations made during the inactive stage of the remittent type of the disease is not significantly different from the mean normal values.

Sedimentation Rate and the Plasma or Serum Protein Components.—The correlation coefficients for the relation between each of the plasma or serum protein components and the sedimentation rate based on 89 observations during varying stages of rheumatic fever are presented in Table 9. The correlation coefficients indicate a significant relation between all components and sedimentation rate, with the exception of beta globulin. The size of the correlation coefficients indicates, however, many individual exceptions to correlation. The correlation coefficients and a study of the scattergrams reveal fibrinogen, albumin, and alpha$_2$ globulin to be correlated more closely with the sedimentation rate than gamma or alpha$_1$ globulin. Changes in the beta-globulin component are apparently not related to the sedimentation rate.

Of 11 observations of the plasma or serum proteins in patients in the late-subacute and inactive stages of the disease with high normal or slightly elevated

TABLE 7.—*Means and Standard Deviations of the Electrophoretic Analysis of Proteins in Plasma or Serum of Patients With Active Chorea Without Other Manifestations of Rheumatic Fever*

	Percentage Composition							Total Proteins, Gm./100 Ml.	Clinical Summary at Time of Observation of Proteins
	Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma' Globulin	Gamma Globulin		
No. patients	5	5	5	5	3	3	5	4	0% with fever; 50% with a functional murmur; erythrocyte sedimentation rate range from 7 to 12 mm., mean 9.8 mm. in 45 min.; interval from onset range 1 to 6 mo., median 3 mo.
No. observations	8	8	8	8	4	4	8	4	
Mean	55.3	5.6	12.1	11.8	5.5	2.2	11.4	7.3	
Standard deviation	1.97	1.49	1.43	2.65	.65	...	2.64	....	

TABLE 8.—*Means and Standard Deviations of the Electrophoretic Analysis of Proteins in Blood or Plasma of Rheumatic-Fever Patients with Remittent Type of Disease According to the Stage of the Disease*

	Percentage Composition							Total Proteins, Gm./100 Ml.	Clinical Summary at Time of Observation of Proteins
	Albumin	Alpha$_1$ Globulin	Alpha$_2$ Globulin	Beta Globulin	Fibrinogen	Gamma' Globulin	Gamma Globulin		
Early-Acute Stage									
No. patients	1	1	1	1	...	1	1	1	1 patient with fever, decompensation; erythrocyte sedimentation rate 96 mm.; interval from onset 1-2 wk.
No. observations	1	1	1	1	...	1	1	1	
Value	37.2	12.9	20.6	7.3	...	0.9	21.1	5.9	
Early-Subacute Stage									
No. patients	1	1	1	1	1	....	1	1	1 patient; several blood transfusions; no fever; murmur present; erythrocyte sedimentation rate 24 mm.; interval from onset 7 mo.
No. observations	1	1	1	1	1	....	1	1	
Value	50.3	5.1	10.0	11.6	6.8	...	16.2	7.0	
Mid-subacute Stage									
No. patients	5	5	5	5	2	4	5	5	5 patients, 9 observations; 22.2% with fever; 88.8% with signs of carditis; erythrocyte sedimentation rate range 6-40, mean 25.9; interval from onset range 5 wk. to 1 yr., median 5 mo.
No. observations	9	9	9	9	4	5	9	9	
Mean	47.4	6.8	12.9	11.8	8.5	3.0	15.6	7.5	
Standard deviation	3.52	1.71	1.68	4.35	...	1.05	3.06	.76	
Late-Subacute or Early-Inactive Stage									
No. patients	6	6	6	6	4	2	6	6	6 patients, 7 observations; 0% with fever; 100% with a residual murmur; erythrocyte sedimentation rate range 6 to 45, mean 20.3; interval from onset range 3.3-15 mo., median 7.5 mo.
No. observations	7	7	7	7	5	2	7	7	
Mean	55.4	5.0	10.6	11.1	5.3	2.9	13.4	7.9	
Standard deviation	3.09	1.25	2.11	2.38	.82	....	1.99	1.99	
Inactive Stage									
No. patients	4	4	4	4	2	2	4	4	4 patients, 4 observations; 0% with fever; 100% with a residual murmur; erythrocyte sedimentation rate range 9-22, mean 13.5 mm. in 45 min.
No. observations	4	4	4	4	2	2	4	4	
Mean	58.7	6.0	8.8	10.9	5.2	3.9	11.1	7.2	
Standard deviation	....	....	....	....	...	....	....	....	

sedimentation rate (range 15 to 31 mm. in 45 minutes), 64% of the albumin values, 38% of the fibrinogen, and the globulins, 18% of the alpha$_1$, 27% of the alpha$_2$, 45% of the beta, 0% of the gamma', and 45% of the gamma values, deviate one standard deviation or more from the mean values of normal children.

When the sedimentation rate had been normal one to seven days, of nine observations 67% showed alterations in albumin, 38% in fibrinogen, and the globulins, 0% in alpha$_1$, 44% in alpha$_2$, 33% in beta, 0% in gamma' and 56% in gamma.

Of 17 observations on patients whose sedimentation rates had been normal from two to seven and one-half weeks, the incidence of alterations in the proteins was 24% in albumin, 21% in fibrinogen, and the globulins, 0% in alpha$_1$, 24% in alpha$_2$, 6% in beta, 0% in gamma', and 12% in gamma.

TABLE 9.—*Correlation Coefficients for Relationship of Erythrocyte Sedimentation Rate and Plasma or Serum Protein Components*

Sedimentation rate versus albumin	—.55
Sedimentation rate versus alpha$_1$ globulin	.43
Sedimentation rate versus alpha$_2$ globulin	.50
Sedimentation rate versus beta globulin	.04
Sedimentation rate versus fibrinogen	.56
Sedimentation rate versus gamma globulin	.43

COMMENT

It is desirable for the clinician as well as for the laboratory scientist to keep in mind that each child with rheumatic fever responds somewhat differently and that numerous variable factors influence the type of response. Since the host plays an important role in rheumatic fever, basic studies which increase our knowledge of the factors that condition the host to a given response to certain noxious stimuli are pertinent. The serum-protein components of children with acute rheumatic fever are altered, and each follows a relatively constant pattern and reverts to normal as the disease regresses and becomes inactive. Measurement of the serum-protein components serves as a sensitive index of disease activity in rheumatic fever, and the alterations observed in different fractions during the course of the disease may reflect changes which are of fundamental value. Although the causes for the alterations of the serum-protein components are understood poorly, we are accumulating knowledge gradually to explain some of the changes in the classical subdivisions of the blood proteins. Various protein acute-phase substances, such as C-reactive protein, mucoproteins, and nonspecific hyaluronidase inhibitor, are known to be present in abnormal amounts in disease and are reported to migrate with the alpha-globulin fractions, whereas the streptococcal antibodies and perhaps homologous tissue antibodies are reported to migrate with the gamma globulin.

A decrease in the level of serum protein, particularly the albumin fraction, has been considered to indicate tissue protein depletion.[5] The mean values of total

5. (*a*) Dodd, K., and Minot, A.: Occurrence of Moderately Reduced Serum Albumin in 500 Children in a Southern Clinic, J. Pediat. **8**:452, 1936. (*b*) Holman, R. L.: Low Protein Diet Augments Hyperproteinemia Produced by Repeated Injections of Homologous Plasma: Evidence for a Dynamic Equilibrium Between Food, Plasma, and Tissue Proteins, J. Exper. Med. **75**:519, 1942. (*c*) Sachar, L. A.; Horvitz, A., and Elman, R.: Studies on Hypoalbumi-

protein in this study do not indicate the presence of hypoproteinemia in any of the groups, with the possible exception of the group of patients having acute rheumatic fever with cardiac decompensation. The mean total protein values for all the subgroups without cardiac decompensation show a tendency to be elevated; the value for the late-subacute stage is significantly elevated. The latter value may reflect the high protein diet of the convalescent patients. The total protein values for each of the subgroups showed somewhat greater variation than the values for normal children, suggesting a disturbance in total protein for some individuals.

The percentage of albumin is markedly decreased in the early- and late-acute stages and also in the early-, mid-, and late-subacute stages. The mean values for the subgroups gradually increase as the disease regresses, but in the late-subacute stage 38% of the values continue to be decreased markedly (deviate two standard deviations or more from the mean of normal children), and the mean value is significantly different from the mean for normal children. Dodd and Minot,[5a] in 1936, reported that a chronic low-grade deficiency in serum proteins, particularly the albumin fraction, was found in children living in adverse environmental conditions, even in the absence of acute or chronic infections, and that with acute or chronic infections the serum albumin rarely reached the normal range, except in the presence of dehydration. Animal studies have shown that there is a small but relatively constant decrease in total circulating plasma albumin when the animals are fed a protein-poor diet for a period of three weeks or more. Recent studies of Chow and co-workers indicated that feeding dogs a protein-free diet over a long period will drain the "reserve protein stores" first, and finally deplete the plasma proteins. Electrophoretic analyses of the sera of four men before and after acute starvation with hard work demonstrate no important changes in blood protein other than a general increase in concentration due to a mild dehydration.[6] These experiments in young adults also demonstrate that protein depletion due to simple undernutrition does not explain the decreased relative albumin and increased alpha globulins shown in the electrophoretic patterns of sera from patients suffering from chronic diseases as rheumatic fever. The decrease in albumin and the increase in alpha globulins are not explicable as a result of simple negative nitrogen balance. However, an inadequate protein intake over a period of time may alter the serum-protein levels in children more readily than in adults, because children have a higher protein requirement for growth and a smaller amount of protein stores in the tissues. Although changes in serum-protein fractions, particularly the hypoalbuminemia observed in our rheumatic-fever patients, may have some relationship to the nutritional status of the child prior to or at the time of the onset of his disease, the changes observed during acute infections are apparently of such magnitude that

nemia Produced by Protein-Deficient Diets: Hypoalbuminemia as a Quantative Measure of Tissue Protein Depletion, ibid. **75**:453, 1942. (*d*) Bieler, M. M.; Ecker, E. E., and Spies, T. D.: Serum Proteins in Hypoproteinemia Due to Nutritional Deficiency, J. Lab. & Clin. Med. **32**:130, 1947. (*e*) Cayer, D., and Nabors, G. C.: Clinical Evaluation of Total Blood Proteins and Albumen and Globulin Fractions in Hospitalized Patients: Analysis of Data in 300 Cases, South. M. J. **40**:744, 1947. (*f*) Chow, B., in Albanese, A. A., Editor: Protein and Amino Acid Requirements of Mammals, New York, Academic Press, Inc., 1950, pp. 94-114.

6. Taylor, H. L.; Mickelsen, O., and Keys, A.: The Effects of Induced Malaria, Acute Starvation, and Semi-Starvation on the Electrophoretic Diagram of the Serum Proteins of Normal Young Men, J. Clin. Invest. **28**:273, 1949.

they tend to mask the smaller changes resulting from tissue-protein depletion related to malnutrition.

Recent studies of Bieler, Ecker, and Spies [5d] showed that the gradual depletion of serum-protein levels which follows chronic uncomplicated malnutrition in adults is probably a relative depletion of all types of protein distinguishable by electrophoretic analysis. Whereas in disease increased amounts of specialized globulins may be produced, in dietary deficiency all types of serum protein may be produced in normal quantitative proportions. They also concluded from their studies of the response of patients with hypoproteinemia that when there was a limited amount of protein available it was used for the production of certain important immunologic elements. The alterations in the serum-albumin component in acute rheumatic fever may be a compensatory mechanism in view of the changes that frequently occur in the globulin components.

The mean values for the percentage composition of $alpha_1$ globulin are significantly increased in both the early- and late-acute stages and are not significantly altered during the later stages of the disease. Forty per cent of the values in the observations are markedly elevated and 40% are slightly elevated or high normal in the early-acute stage. The alterations in the mean values of $alpha_2$ globulin are significant during the early-acute, late-acute, early-subacute, and mid-subacute stages, and a lesser degree of alteration persists in the mean value through the late-subacute stage. The mean value of $alpha_2$ globulin gradually decreases as the disease regresses. C-reactive protein is a protein not normally present in the blood, which occurs during the acute stage of rheumatic fever, but disappears in the late-acute or early-subacute stage of the disease. It is reported to be an alpha globulin. The transient elevation of $alpha_1$ globulin suggests that the C-reactive protein may be in this fraction. The M-antigen and the M-proteins have been extensively studied because of the known relationship between the M-antigen and the virulence of the Group A streptococci. There seems little doubt that the M_2 fraction is a component of the $alpha_1$ globulin, but the M_1 fraction has not been so definitely classified.

Serum mucoproteins of patients with rheumatic fever and of patients included in this study are elevated markedly in the acute stage of the disease and gradually decrease to normal values during the subacute stage. Electrophoretic studies in our laboratories of mucoproteins from patients with rheumatic fever have shown that they migrate as alpha globulins.[7] A high degree of correlation is observed between the level of mucoproteins and $alpha_2$ globulins during the varying stages of the disease, suggesting that the mucoproteins are in the $alpha_2$ fraction of the serum. This suggestion is strengthened by the report of Seibert and co-workers [8] that of the protein fractions isolated from normal plasma the $alpha_2$ globulin has the highest polysaccharide content.

Nonspecific heat-labile hyaluronidase inhibitor belongs to the mycolytic enzyme systems and is known to be increased significantly during the acute phase of many diseases, including rheumatic fever. It is stated that it migrates as an albumin or

7. Levy, L.: Studies on the Mucoproteins of Blood, Thesis, State University of Iowa, 1952.

8. Seibert, F. B.; Seibert, M. V.; Atno, A. J., and Campbell, H. W.: Variation in Protein and Polysaccharide Content of Sera in the Chronic Diseases, Tuberculosis, Sarcoidosis, and Carcinoma, J. Clin. Invest. **26**:90, 1947.

alpha globulin. The serum level of this substance is reported to be consistently lower than normal during the subacute stage of rheumatic fever and for months after the disease is considered inactive.

It has been stated that alpha$_1$ and alpha$_2$ globulins are elevated in relation to febrile conditions. In these rheumatic subjects, elevation of alpha$_1$ globulin is certainly present in the subgroups in which there was fever. It is doubtful if fever per se accounts for the total alteration of alpha$_2$ globulin in the subacute groups, since those with exacerbations and recent infections were excluded from the group and the percentage of the group febrile is 21.4 for the early-subacute and 11.4 for the midsubacute stage.

The mean values for the percentage composition of the beta-globulin component in the varying stages of the disease are not significantly different from the mean values of normal children. A tendency toward slightly elevated values in the late-subacute stage and in chronic decompensation was observed. Two of the three observations of beta globulin in the early-acute stage with cardiac decompensation were definitely low. There is a fairly wide range of values in the total group—from 4.0 to 21.6%. In studies of patients with nephrosis and uncontrolled diabetes mellitus, beta globulin is high, and it is thought to be related possibly to the presence of a labile lipoprotein.[9] The alterations in the beta-globulin component may be related to fat metabolism. The values for the subjects in the subacute stage were investigated to determine whether the alterations were related to excessive weight gains; however, no correlation was evident. Cholesterol is lowered in acute infection and may be related to the low beta-globulin values found for patients in the acute stage with cardiac decompensation.

The mean fibrinogen values are markedly elevated in the acute stage and gradually decrease as the disease regresses. This component is obtained for plasma specimens only. The gamma′-globulin fraction migrates with the fibrinogen fraction in plasma specimens. Part of the elevation in fibrinogen could be due to elevated gamma′ globulin, but not all, since serum specimens do not show elevation in gamma′ globulin great enough to account for the total elevation of fibrinogen. Changes in fibrinogen content are correlated with changes in the erythrocyte sedimentation rate and possibly with other as yet unknown alterations in the host.

As stated previously, some of the electrophoretic values reported in this study are obtained from plasma while others are from sera. Franklin and co-workers[10] studied the electrophoretic patterns of paired serum and plasma samples of 66 persons with various hepatic or miscellaneous diseases and of normal subjects. They found that aside from the significant serum-plasma difference in gamma globulin, the other protein components present were essentially similar in serum and plasma when expressed as grams per 100 ml. Fibrinogen values were markedly elevated, particularly in the groups with cirrhosis of the liver. This was due to the inclusion of a gamma′-globulin fraction in the "fibrinogen" peak. This was

9. Routh, J. I.; Knapp, E. L., and Kobayashi, C. K.: Electrophoretic Studies of Plasma and Urinary Proteins in Children with Lipoid Nephrosis, J. Pediat. **33**:688, 1948.

10. (*a*) Franklin, M.; Bean, W. B.; Paul, W. D.; Routh, J. I.; Huerga, J. de la, and Popper, H.: Electrophoretic Studies in Liver Disease: Comparison of Serum and Plasma Electrophoretic Patterns in Liver Disease, with Special Reference to Fibrinogen and Gamma Globulin Patterns, J. Clin. Invest. **30**:718, 1951; (*b*) Electrophoretic Studies in Liver Disease: Gamma$_1$ Globulin in Chronic Liver Disease, ibid. **30**:729, 1951.

also responsible for the serum gamma globulin being significantly greater than the plasma gamma globulin. The addition of gamma′ as determined by serum to the total plasma gamma globulin yielded total gamma globulin values essentially similar to those of the serum. At the same time subtraction of gamma′ from the elevated fibrinogen values as revealed by the plasma patterns reduced these values approximately 35 to 45%. In our analysis of the gamma globulin we have recorded gamma′ and gamma separately. The authors quoted above add gamma′ to gamma to get the total gamma-globulin fraction. The gamma globulin of serum and plasma are equivalent. "Fibrinogen" of plasma includes gamma′ which is 40 to 45% of "fibrinogen" in liver disease and a varying percentage in rheumatic fever according to the stage of the disease. Since gamma′ globulin is not observed to be increased on the average in other than the acute stages for rheumatic-fever patients, cognizance of its influence on the gamma partition and fibrinogen needs to be taken in the acute stage. Only one gamma′-globulin value is recorded for patients with cardiac decompensation. This value is elevated, 4.7%. If elevation of gamma′ globulin reflects liver disease, then one would expect to find elevation of gamma′ globulin for patients with passive congestion of liver. Unfortunately the electrophoretic patterns for all patients with cardiac decompensation are of plasma, and gamma′ peak is obscured by the fibrinogen peak, so our data are incomplete for gamma′ in this important subgroup.

Analysis of the 60 serum samples for gamma′ globulin for these rheumatic-fever subjects in all stages of the disease showed eight values above 4%, the upper limit of normal.[10a] These samples were from four children in the acute stage of the disease, three children with remittent type of the disease at the time of an exacerbation, and one child with inactive rheumatic fever who had had a mild intercurrent infection 10 days prior to the time the specimen was obtained. The highest gamma′-globulin value in the group is 5.3%.

The gamma-globulin values are markedly altered in the active stages of the disease, and the mean values of the different stages of the disease show very little tendency to decrease until the midsubacute stage. In the early-subacute stage the largest percentage of elevated values (markedly or moderately) of gamma globulin is observed. In the late-subacute stage the mean gamma-globulin value is still definitely different from the mean values of normal children. The mean value of the inactive group is not significantly different from the mean of normal children, but 35% of the values are slightly elevated. Anderson, Kunkel, and McCarty [11] reported the occurrence of consistently higher mean values for the two antibodies, antistreptolysin and antistreptokinase, as well as for the gamma-globulin levels in their group of patients with rheumatic fever as compared with the following groups: (1) uncomplicated scarlet fever, single type of Streptococcus; (2) uncomplicated scarlet fever, multiple type of Streptococcus; (3) penicillin-treated scarlet fever. The authors concluded that on the average patients in whom rheumatic fever developed as a sequela to a streptococcal infection exhibited a greater antibody response than those in whom rheumatic fever did not develop. The greater production of the two antibodies in those patients in whom rheumatic fever developed is a

11. Anderson, H. C.; Kunkel, H. G., and McCarty, M.: Quantitative Antistreptokinase Studies in Patients Infected with Group A Hemolytic Streptococci: A Comparison with Serum Antistreptolysin and Gamma Globulin Levels with Special Reference to the Occurrence of Rheumatic Fever, J. Clin. Invest. **27**:425, 1948.

reflection of a general augmentation of antibody formation. In the electrophoretic patterns of the plasma or serum proteins of rheumatic-fever patients in our study the elevation of the gamma-globulin component is interpreted as a reflection of the augmented antibody production. This is in accord with the earlier findings of Dole and co-workers and in conflict with the findings of Wilson and Lubschez.

For many years the erythrocyte sedimentation rate has been used as an index of rheumatic activity in rheumatic fever patients. The correlation coefficients are higher for the relation between the sedimentation rate and fibrinogen, albumin, and alpha$_2$ globulin than for the relation between sedimentation rate and gamma and alpha$_1$ globulins. There is no correlation indicated between beta globulin and sedimentation rate. In the late-subacute stage when the erythrocyte sedimentation rate had been normal one to seven days, slight alterations in the albumin, alpha$_2$-globulin, and gamma-globulin components were found in approximately one-half of the observations.

The slower response to therapy of the patients with cardiac decompensation is reflected in the alterations of the protein components, particularly the albumin and gamma-globulin fractions. Stadler and Stinger [12] state that the cells of the liver having to do with albumin formation are susceptible to the effects of passive congestion of that organ.

The alterations in the blood protein in patients with chorea without manifestations of rheumatic fever are additional evidence that chorea is a manifestation of rheumatic fever. The elevation of the alpha$_2$-globulin fraction observed cannot be explained by the presence of C-reactive protein or an elevation in the level of mucoproteins, as patients with severe chorea with no manifestations of rheumatic fever and with normal sedimentation rates have shown no C-reactive protein and normal mucoprotein values. Patients with uncomplicated chorea and inactive rheumatic fever for six months or more have been reported with mean hyaluronidase inhibitor levels significantly lower than those found in normal children. Jacox [13] found that cationic detergents, used as a test for acute-phase protein, will react with serum and remove the alpha$_1$ and alpha$_2$ globulins as determined by electrophoretic studies. They also observed several patients with chorea who had normal sedimentation rates in whom the turbidity reaction measured by these detergents was strongly positive.

In the inactive group of patients the mean values of the percentage composition of the protein components of the serum were found to be not significantly different from the values for the normal group. This, however, is not evidence that rheumatic susceptibility has no relationship to altered proteins, since the inactive patients in the study group had been receiving a much better diet than most of the rheumatic patients who come under care directly from their homes. The data do show that, as a group, the rheumatic-fever subjects are capable of normal protein metabolism.

SUMMARY

In the adjustment of the child to acute disease a number of changes occur in the serum protein components of the blood in addition to the antibody response.

12. Stadler, H., and Stinger, D.: A Case of Pick's Syndrome as the Basis for a Study of Hypoproteinemia, J. Pediat. **18**:84, 1941.

13. Jacox, R. F.: The Reaction of Human Serum and Component Proteins of Human Plasma with a Quaternary Ammonium Salt, Octab, J. Lab. & Clin. Med. **37**:721, 1951.

This study is a report of our data on the alterations in 77 children with definite rheumatic fever treated by standard nonspecific therapy, and 5 patients with chorea without other manifestations of rheumatic fever. The protein components of 205 plasma or serum specimens are analyzed in relation to the course of the disease. A definite pattern was found which may provide a baseline for future studies.

The percentage composition of albumin, fibrinogen, and the globulins, alpha$_1$, alpha$_2$, gamma′, and gamma is markedly altered in the acute stage of the disease. The return to normal mean values as the disease regresses is gradual for albumin, fibrinogen and alpha$_2$ and gamma globulins; alpha$_1$ and gamma′ globulins are elevated generally only in the acute stage. Changes in the percentage composition of beta globulin are not correlated with the stages of the disease; the mean values for total proteins are slightly elevated for all subgroups of uncomplicated rheumatic fever and significantly elevated in the late-subacute stage. The mean values of serum-protein fractions for the group of inactive rheumatic-patients indicate that the rheumatic-fever patients as a group are capable of normal protein metabolism. The pattern of alteration of the percentage composition of each of the classical serum or plasma components is discussed in relation to some of the known acute-phase reactions, tests, and antibody production.

NEW TREATMENT FOR ATELECTASIS OF THE NEWBORN

WILLIAM G. LOVE Jr., M.D.
AND
BERT TILLERY, M.D.
COLUMBUS, GA.

A SIMPLE method of treatment of one type of persistent atelectasis of the newborn infant will be presented. It is based on a familiar but frequently unrecognized cause of atelectasis in the premature infant. The treatment is patterned after that found effective for a somewhat similar physiological disturbance observed in the adult with "steering wheel" fractures of the sternum.

The necessity of improved therapy in atelectasis of the newborn infant has been emphasized recently in a review of neonatal mortality by Bundesen [1] and co-workers. They found that "abnormal pulmonary ventilation is the leading cause of death in the newborn, accounting for 47% of all deaths."

The etiological concept upon which our treatment is based was presented by Wilson and Farber,[2] who noted that often in the newborn infant, and more frequently in the premature, a retraction of the chest wall occurred with each diaphragmatic contraction. They felt that the immature cartilageous chest wall did not furnish an effective scaffolding to counter the strong diaphragmatic contractions. Thus, much of the effectiveness of the diaphragmatic action in expanding the thorax of these infants was offset by the retraction of the chest wall. They were unable to demonstrate tracheal or bronchial obstruction in these infants.

From clinical observation it occurred to us that this was quite similar to the picture observed in adults who had "steering wheel" fractures of the sternum and ribs. The treatment for these adults consisted of sternal traction, and sometimes costal traction, to fix the flaccid chest wall.

It seemed logical to apply this method to infants with persistent atelectasis who evinced marked costal and sternal retraction with inspiratory efforts. Its effectiveness, simplicity, and harmlessness had been amply demonstrated in the adult, and its application to infants has proved even more simple.

The skin and fascia overlying the lower end of the sternum is caught with a towel clip. Traction is applied through the medium of small rubber bands attaching the handle of the towel clip to the top of the incubator. An additional clip (or clips) is placed on the skin and fascia overlying the ribs, if this seems necessary to control retraction. The response is frequently immediate, with gratifying disappearance of cyanosis and a striking increase in the effectiveness of inspiration.

1. Bundesen, H. N., and others: Progress in Reduction of Needless Neonatal Deaths: Challenge to Health Officers and Medical Profession, J. A. M. A. **148**:907, 1952.

2. Wilson, J., and Farber, S.: Pathogenesis of Atelectasis of the New Born, Am. J. Dis. Child. **46**:590, 1933.

This traction will hold for a period of 24 to 72 hours. During this time the improved expansion will overcome the cohesion of moist surfaces of the collapsed alveoli and allow pulmonary inflation. Once this is attained, a lesser negative pressure is sufficient to maintain satisfactory aeration. In our experience, even the smaller premature infants are capable of maintaining expansion once it is accomplished. This has been demonstrated experimentally by Wilson and Farber. They found that particularly high negative pressures were necessary, in the beginning, to overcome the cohesion of the moist surfaces of the collapsed and airless alveoli. However, once pulmonary expansion was attained, far less effort was necessary to maintain adequate pulmonary exchange.

Berglund and Eder [3] confirmed this fact clinically in their cases in which the initial expansion was obtained by open thoracotomy and application of positive pressure via the trachea.

In the treatment of injured adults we have used tracheotomy and repeated tracheal aspirations when excessive mucus accumulated or when atelectasis had occurred. We have not had occasion to utilize tracheotomy in the infant, but would do so if clinical signs appeared to warrant its application.

The following is a report of a case in which sternal traction was used effectively.

C. D. S., a premature baby boy, birth weight 4 lb. 2 oz. (1,870 gm.), was delivered spontaneously after normal labor at 2:30 a.m. on Jan. 12, 1951.

Although respirations began spontaneously, a general cyanosis persisted until the child was placed in an incubator shortly after delivery. Moderate sternal retraction on inspiration was evident from the onset of respiration. By 8:30 a.m. the cyanosis became more marked despite high oxygen concentration within the incubator. The respiration had become more rapid and sternal retraction became strikingly apparent. Moderate clearing of cyanosis occurred at intervals, usually during episodes of crying.

On the following day, Jan. 13, 1951, the respirations were more labored and cyanosis more evident. At 3 p.m., caffeine was given at intervals and caused slight improvement. At 9 p.m. the child had a short period of apnea. This lasted until the cyanosis became intense and was terminated by quick, strong, irregular, gasping inspirations. This served to relieve the cyanosis temporarily and was supplanted by the rapid laboring respiration which had characterized the earlier course. Respirations gradually became more labored, and the cyanosis slowly deepened.

Another episode of apnea occurred at 3 a.m. on Jan. 14, 1951. At this time traction was applied to the skin and fascia over the lower end of the sternum by means of a towel clip which was supported from the top of the incubator by rubber bands threaded through the handle. The patient's condition improved immediately, and cyanosis disappeared gradually and steadily during the next 12-hour interval. The skin-and-fascia traction was quite effective in immobilizing the sternum for a period of 24 hours. Some sternal retraction was evident on release of the traction at this time. Fear of recurrence of atelectasis prompted us to reapply sternal traction in an adjacent area. This time, small incisions were made with a stab blade at either margin of the sternum and the points inserted through the incisions to engage the presternal fascia.

Feedings were begun at this time and increased as improvement continued. The sternal traction was maintained for six days. No sternal retraction occurred with the release of traction. The infant was dismissed from the hospital on Feb. 9, 1951, weighing 5 lb. 5 oz. (2,410 gm.). When the child was last seen, a year later, there was no depression of the sternum, and the only stigma of his treatment was a small scar overlying the sternum.

3. Berglund E., and Eder, W. P.: A Surgical Approach to Atelectasis of the New Born Infant: Preliminary Report, Surgery **29**:127, 1951.

This report is published in the hope that the simplicity of the procedure will warrant its trial by many who, like ourselves, do not have access to the complicated and costly negative pressure respirators now in use. Further, the method of treatment by sternal traction does appear to offer one distinct advantage over the method of treatment of atelectasis with mechanical respirators; namely, bronchial dilatation occurs with spontaneous inspiration; it does not occur when respiration is mechanically contrived.

SUMMARY

Atelectasis in the newborn infant is occasionally due to underdevelopment of the ribs and costal cartilages.

The high negative intrathoracic pressures required to overcome the cohesion of the moist alveoli surfaces of the atelectatic lung cannot be attained without assistance in these infants.

A traction method of sternal stabilization, similar to that used in adults with fractured ribs and sternum, is advised in the treatment of the newborn infant who manifests sternal retraction and cyanosis in the neonatal period.

GROWTH AND METABOLISM IN NORMAL AND THYROID-ABLATED INFANT RHESUS MONKEYS (MACACA MULATTA)

V. Roentgenographic Features of Skeletal Development in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta)

LEE B. LUSTED, M.D

DONALD E. PICKERING, M.D.

DELBERT FISHER, M.D.

AND

FRANCIS SCOTT SMYTH, M.D.

SAN FRANCISCO

IT IS THE purpose of this paper to integrate roentgenologic features of skeletal growth and development in normal and athyroid infant rhesus monkeys with previously reported studies of growth and metabolism in the same animals.[1]

In the present study, skeletal growth and maturation were evaluated by serial roentgenograms. The roentgenologic features of thyroid deficiency in humans are well described.[2] These features, however, have not previously been investigated in subhuman primates.

METHODS AND MATERIALS

Animals.—Six infant rhesus monkeys whose lineage was carefully recorded were obtained for our studies from the indoor macaque colony of Dr. van Wagenen at Yale University.[1a]

This investigation was principally supported by a research grant from the Playtex Park Foundation to the Department of Pediatrics.

From the Department of Radiology, American Cancer Society Fellow in Radiology (Dr. Lusted), and Department of Pediatrics of the University of California School of Medicine.

1. (*a*) Pickering, D. E.; Smyth, F. S.; van Wagenen, G., and Fisher, D. A.: Growth and Metabolism in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta): I. Growth and Metabolism in Normal Infant Rhesus Monkeys (Macaca Mulatta), A. M. A. Am. J. Dis. Child. **86**:1, 1953. (*b*) Pickering, D. E., and Fisher, D. A.: II. Growth and Metabolism in Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid. **86**:11, 1953. (*c*) Pickering, D. E., and Fisher, D. A.: III. Growth and Metabolism Following *l*-Thyroxine Administration in Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid., **86**:147, 1953. (*d*) Pickering, D. E.; Fisher, D. A., and Scott, K. G.: IV. Radiosodium (Na^{24}) Space in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid. **86**:157, 1953. (*e*) Pickering, D. E.; Fisher, D. A., and Scott, K. G.: VI. Iodine Metabolism in Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid., to be published. (*f*) Crane, J.; Pickering, D. E., and Smyth, F. S.: VII. Histopathology of Normal and Thyroid-Ablated Infant Rhesus Monkeys (Macaca Mulatta), ibid., to be published.

2. Caffey, J.: Pediatric X-Ray Diagnosis: Textbook for Students and Practitioners of Pediatrics, Surgery & Radiology, Chicago, Year Book Publishers, Inc., 1950. Schinz, H. R.; Baensch, W. E.; Friedl, E., and Uehlinger, E.: Roentgen-Diagnostics, English translation of Fifth German edition edited by J. T. Case, Vol. II, New York, Grune & Stratton, Inc., 1952. Wilkins, L.: The Rates of Growth, Osseous Development, and Mental Development in Cretins as a Guide to Thyroid Treatment, J. Pediat. **12**:429, 1938.

Animals D-766 and C-794 were used as controls throughout the study, while Animal B-767 was used as a third normal control until the age of 162 days at which time it received a thyroid-ablating dose of 1.5 mc. of I^{131}.[1b] Animal B-767 was thereafter included in the thyroid-ablated group. Another animal, S-775, was similarly rendered athyroid at the age of 122 days.[1b] Two additional animals, A-791 and P-790, underwent complete I^{131} thyroid ablation at 22 and 35 days, respectively. Completeness of ablation had been confirmed in all animals by demonstrating (*a*) the lack of concentration of I^{131} in the anatomical area of the thyroid [1b]; (*b*) a marked and sustained drop in their serum precipitable iodine values to below 1 γ per 100 cc.[3]; and (*c*) the absence of detectable thyroid tissue histologically in Animals S-775 and P-790 which were electively sacrificed.[1f] Parathyroid function remained normal in all animals, and normal-appearing parathyroid glands were found at autopsy examination of animals S-775 and P-790.[4] The effects of thyroid ablation were studied over a four-month period in all animals. Subsequently, the effects of replacement therapy with crystalline *l*-thyroxine were evaluated over a similar period. Table 1 presents data on age at which thyroid was ablated and time of therapy with *l*-thyroxine.

The general effects of I^{131} thyroid ablation and of therapy with *l*-thyroxine on growth and metabolism will be reviewed briefly.[5]

The physical features of the athyroid infant monkeys generally resembled those of human cretins. They developed thickened myxedematous skin, their hair was coarse and dull, their

TABLE 1.—*I^{131} Thyroid Ablation and l-Thyroxine Therapy*

Animal	I^{131} Thyroid Ablation, Age in Days	Age (Days) During *l*-Thyroxine Therapy	
		6γ/Kg./Day *	20γ/Kg./Day *
A-791	22	.....	153-243
P-790	35	107-257	.....
B-767	162	.....	317-428
S-775	122	.....	.....

* Dosage given.

abdomens were protuberant, and umbilical hernias were present. Macroglossia was prominent, and eruption of deciduous teeth ceased following thyroid ablation.

The above features of athyrosis disappeared within 45 days after institution of long-term replacement therapy with either 6 or 20 γ per kilogram of body weight per day of *l*-thyroxine.

In normal animals, weight gain stabilized at 10 ± 1 Gm. per kilogram of body weight per day at 30 to 40 days of age and thereafter declined at a slow and uniform rate.[1a] At 140 days weight gain was 5 ± 1 Gm. per kilogram per day. Voluntary caloric intake was similarly uniform among animals, and declined from 300 ± calories per kilogram per day at 30 to 40 days to 200 ± calories per kilogram per day at 140 days. Food made available (by bottle feeding) was of uniform composition and ratios among food elements (carbohydrate, fat, protein, calcium, and phosphorus) remained constant.

In contrast to normals, gain by the athyroid group ceased 30 to 45 days following I^{131} thyroid ablation, their weights thereafter remained plateaued,[1b] and voluntary caloric intake decreased 50%. Following institution of therapy with either 6 or 20 γ per kilogram per day of *l*-thyroxine, weight gain became active and accelerated to normal by 75 days. Caloric intake also increased to normal.

Over the same period retentions in normal animals on a mg. per kilogram of body weight per day basis averaged 635 nitrogen, to 135 calcium, to 117 phosphorus. Retentions by athyroid animals were markedly reduced from normal and fluctuated with the degree of myxedema.

3. Footnotes 1 *b* and *c*.

4. Footnotes 1 *b* and *f*.

5. Footnotes 1 *a*, *b*, and *c*.

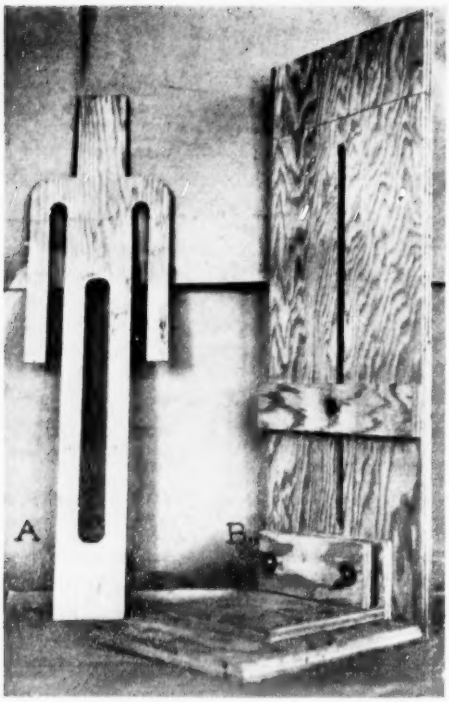


Fig. 1.—*A*, monkboard. *B*, platform support for monkboard.

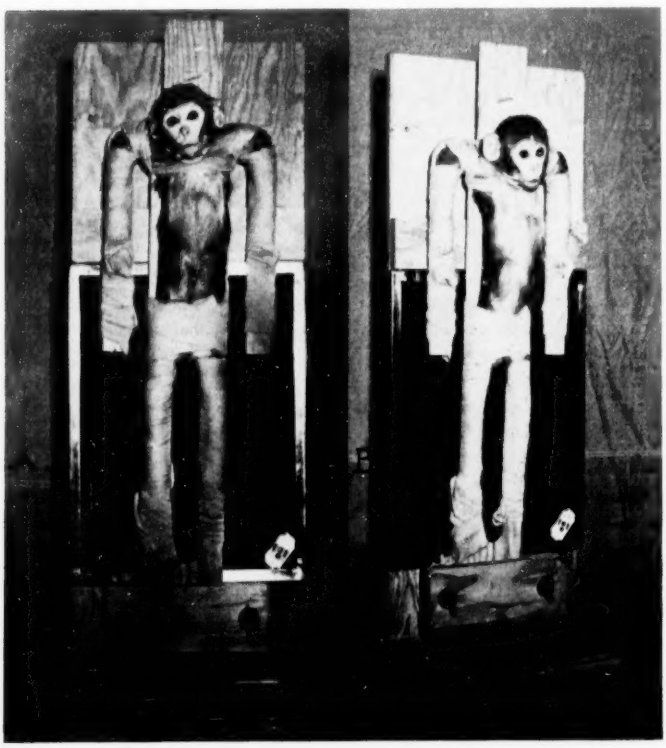


Fig. 2.—Monkboard with animal and film cassette in position. *A*, front view. *B*, oblique view.

With therapy, nitrogen, and phosphorus retention returned to normal, while that of calcium remained at approximately 50% of expected levels. The difference between observed and expected calcium retention was presumed to be related to calcium made available by reorganization of overly calcified bone.

Roentgen Technique.—Techniques were designed to permit standardized serial (30-day) roentgenograms without animal anesthesia—accomplished through use of methods devised by

Fig. 3.—Representative total body roentgenogram.

Miller [6] (Fig. 1). Animals were secured to the "Monkboard" with Ace bandages and positioned upright with casettes appropriately mounted (Fig. 2).

Films were taken at a target film distance of 6 feet (183 cm.), 100 ma., 1/20 second, and with 60 to 70 kv. A representative roentgenogram is shown in Figure 3.

Linear growth was evaluated by measurement of diaphysial and total length of the left tibia and femur. Measurements of individual roentgenograms were reproducible with an error of not more than 1 mm.

6. Miller, E. R.: A Device for Immobilizing Children During Radiographic Examination, Radiology **58**:421, 1952.

Maturation was evaluated by serial counts of centers of ossification listed below.

Ossification Centers in Left Side of the Skeleton Which Were Counted (Total, 68)

I. Shoulder (2):
- Humerus—proximal medial epiphysis
- Humerus—proximal lateral epiphysis

II. Elbow (3):
- Capitellum ulna
- Radius—proximal epiphysis
- Olecranon

III. Wrist and Hand (29):
- Ulna—distal epiphysis
- Radius—distal epiphysis
- Capitate
- Hamate
- Triquetrum
- Lunate
- Scaphoid
- Pisiform
- Trapezium
- Trapezoid
- Distal phalangeal epiphyses (5)
- Middle phalangeal epiphyses (4)
- Proximal phalangeal epiphyses (5)
- Metacarpal epiphyses (5)

IV. Hip (2):
- Femur—proximal epiphysis
- Femur—greater trochanter

V. Knee (4):
- Femur—distal epiphysis
- Patella
- Tibia—proximal epiphysis
- Fibula—proximal epiphysis

VI. Ankle and Foot (28):
- Tibia—distal epiphysis
- Fibula—distal epiphysis
- Cuboid
- Navicular
- Calcaneum
- Talus
- Cuneiforms (3)
- Distal phalangeal epiphyses (5)
- Middle phalangeal epiphyses (4)
- Proximal phalangeal epiphyses (5)
- Metatarsal epiphyses (5)

RESULTS AND COMMENT

Growth and developmental data collectively presented in Table 2 are discussed under three headings: Long Bone Growth; Epiphyseal Maturation, and Skull Development.

Long Bone Growth.—Linear growth of long bones in the normal animals was uniform. The increment of tibia and femur length is presented with data relating the rate of body weight gain and correlated voluntary caloric intake for normal infants over the period indicated (Fig. 4). It will be noted that tibia and femur lengths increased approximately 20 mm. during the 100-day period between the ages of 60 and 160 days, with femur growth somewhat greater than that of the tibia.

The rate of linear bone growth in the athyroid animals slowed remarkably within 30 days following I^{131} thyroid ablation and was closely allied with the plateau in body weight and other features reviewed earlier. The rates of linear bone growth following thyroid ablation in Animals A-791 and P-790 are graphically shown with data depicting effected rates of body weight gain and caloric intakes (Fig. 5). In contrast to the 20 mm. linear increment in normals, tibia and femur length in the athyroid animals increased by approximately 10 mm. during a chronologically comparable period. Much of this growth followed the single administration of 250 γ per kilogram of *l*-thyroxine to Animals A-791 and P-790 at approximately 100

days of age—a dose shown to have demonstrated significant though transient metabolic effects and elevated serum precipitable iodine levels for approximately 15 days.[3]

TABLE 2.—*Growth Data on Infant Macaque Monkeys (All Femur and Tibia Measurements in Centimeters)*

Animal D-766 (age, days)	61	91	128	160	193	229	273	313	344	372	407	438
Femur—diaphysis	6.4	6.8	7.5	8.1	8.7	9.0	9.5	9.6	9.8	10.2	10.6	10.6
—total	7.2	7.7	8.6	9.3	9.9	10.4	10.6	11.1	11.4	11.4	11.8	11.9
Tibia —diaphysis	5.7	6.4	7.0	7.6	8.1	8.4	9.0	9.3	9.5	9.6	9.8	10.2
—total	6.5	7.1	7.8	8.2	8.9	9.3	9.7	10.1	10.3	10.5	10.6	10.8
No. epiphyseal centers	64	66	66	66	66	68	68	68	68	68	68	68
Animal B-767 (age, days)	59	89	126	158	191	227	271	311	342	370	405	436
Femur—diaphysis	6.6	7.3	8.0	8.5	8.5	8.8	8.8	8.9	9.1	9.5	10.0	10.1
—total	7.6	8.1	9.0	9.6	9.6	9.8	9.8	10.0	10.3	10.5	11.0	11.4
Tibia —diaphysis	6.4	6.8	7.6	8.0	8.3	8.4	8.6	8.7	8.9	9.0	9.6	9.8
—total	7.1	7.5	8.3	8.7	9.0	9.1	9.2	9.3	9.6	9.8	10.3	10.6
No. epiphyseal centers	64	66	66	66	67	67	67	68	68	68	68	68
Animal S-775 (age, days)	28	60	97	129	162	198	242	282	313	341		
Femur—diaphysis	5.2	6.3	6.9	7.1	7.6	7.6	7.6	7.6	7.6	7.8		
—total	6.4	7.0	7.9	8.1	8.5	8.5	8.5	8.5	8.6	8.8		
Tibia —diaphysis	5.2	5.9	6.4	6.7	6.9	7.0	7.0	7.3	7.3	7.4		
—total	5.8	6.5	7.1	7.4	7.4	7.6	7.7	8.0	8.0	8.0		
No. epiphyseal centers	60	64	65	65	65	65	65	65	66	67		
Animal A-791 (age, days)	50	84	124	151	182	217	248	278				
Femur—diaphysis	5.7	5.8	5.8	6.0	6.5	7.2	7.8	8.0				
—total	6.4	6.5	6.8	6.9	7.4	8.3	8.8	8.9				
Tibia —diaphysis	5.3	5.5	5.8	5.8	6.1	6.8	7.2	7.2				
—total	5.9	6.0	6.2	6.3	6.8	7.4	7.8	7.9				
No. epiphyseal centers	62	63	64	64	66	67	67	67				
Animal P-790 (age, days)	64	98	138	165	196	231	262	292				
Femur—diaphysis	6.0	6.2	6.5	6.6	7.1	7.3	7.8	7.8				
—total	6.7	7.0	7.5	7.5	8.1	8.3	8.8	8.8				
Tibia —diaphysis	5.5	6.0	6.4	6.4	6.6	6.8	7.5	7.5				
—total	6.2	6.6	7.0	7.0	7.2	7.4	8.1	8.2				
No. epiphyseal centers	63	63	63	63	65	66	66	66				
Animal C-794 (age, days)	26	66	97	128	163	194	224					
Femur—diaphysis	5.4	6.3	7.0	7.6	8.0	8.4	8.9					
—total	6.1	7.1	7.7	8.5	9.0	9.4	9.8					
Tibia —diaphysis	5.2	6.2	6.8	7.3	7.8	8.3	8.6					
—total	5.7	6.9	7.5	7.9	8.6	9.0	9.3					
No. epiphyseal centers	61	63	65	66	67	68	68					

Thyroid ablation in older animals similarly slowed the rate of linear bone growth within 30 days; Animals B-767 and S-775, ablated at 162 and 122 days, respectively, experienced marked slowing in tibial and femur growth. Increment in length of tibia and femur by those animals is compared to that of normal Animal D-766 over a 90-day period beginning 30 days after thyroid ablation (Table 3).

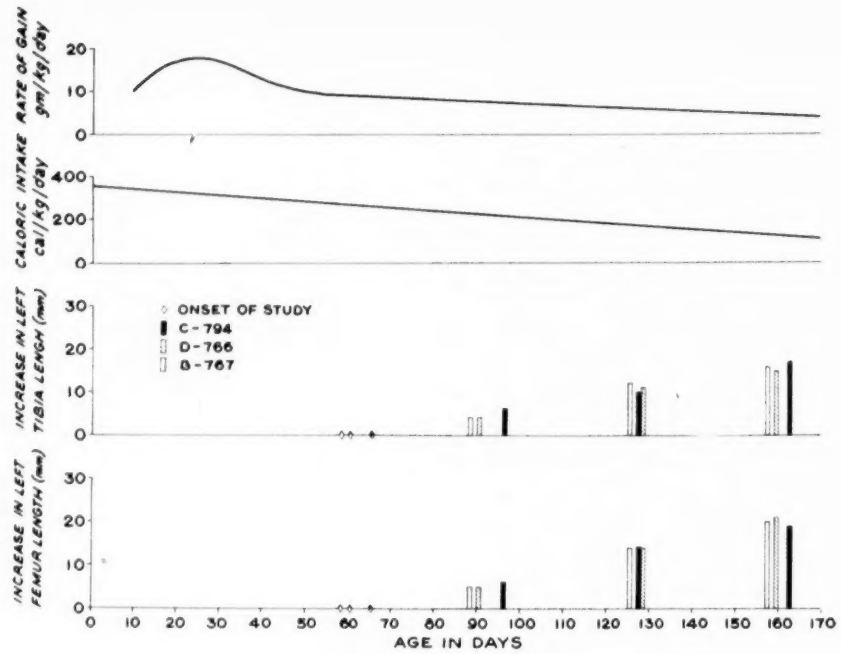


Fig. 4.—Left femur and tibia growth in normal macaque infants.

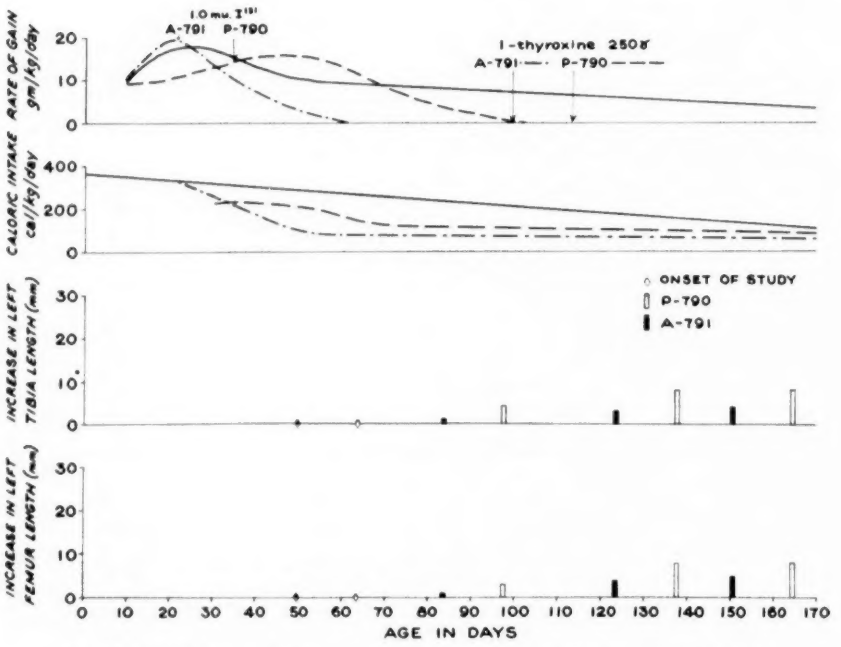


Fig. 5.—Left femur and tibia growth in athyroid (I^{131}-ablated) macaque infants.

It will be noted that while the increment of tibia and femur length was markedly reduced following thyroid ablation, there was continued slow growth in all four animals.

Bone density as well as long bone growth appeared to be altered in athyroid animals. This was borne out by densimeter measurements of tibia and carpal bones which revealed bone density 1.5 times normal in the athyroid group.[7] Histopathological examination of the long bones of Animals P-790 and S-775 also revealed increased bone density.[1f]

Dosage and duration of replacement therapy with *l*-thyroxine for all animals has been presented in Table 1. In a previous communication it was pointed out that the metabolic requirements by tissues other than bone were adequately met by administration of 6 or 20 γ per kilogram per day. The present study reveals a differential effect on bone by those doses. As seen in Figure 6, therapy with 20 γ per kilogram per day of *l*-thyroxine was followed by resumption of normal tibia and femur growth in Animal A-791, whereas Animal P-790, receiving 6 γ per kilogram per day, manifested a much poorer response.

TABLE 3.—*Long-Bone Growth in Normal and Athyroid Macaques*

Animal	State	Age, Days	Bone Length, Cm.		Growth, Cm.	
B-767	Athyroid	191 *	Femur	9.6		
			Tibia	9.0		
		271	Femur	9.8	Femur	0.2
			Tibia	9.2	Tibia	0.2
S-775	Athyroid	162 *	Femur	8.5		
			Tibia	7.4		
		242	Femur	8.5	Femur	...
			Tibia	7.7	Tibia	0.3
D-766	Euthyroid	193 *	Femur	9.9		
			Tibia	8.9		
		273	Femur	10.6	Femur	0.7
			Tibia	9.7	Tibia	0.8

* 30 days following I^{131} thyroid ablation.

Animal B-767, on 20 γ per kilogram per day, similarly resumed a normal rate of bone growth by 30 days.

Epiphyseal Maturation.—Delayed appearance and retarded development of epiphyseal centers of ossification were observed in the athyroid animals. Approximately 60 epiphyseal centers were present in the normal animals by 26 days of age, and 68 centers had appeared by 220 days (see list).

Athyroid Animals A-791 and P-790 showed very few new epiphyseal centers between the time of thyroid ablation and institution of therapy (Tables 1 and 2).

Animal B-767 had 67 of 68 centers present when the thyroid was ablated at 162 days, and therefore little of the effect on epiphyseal maturation was noted in that animal. Animal S-775 showed no substantial increase over and above the 65 centers present when ablated at 122 days (Tables 1 and 2).

In conclusion, a delayed appearance of secondary centers of ossification was noted when I^{131} thyroid ablation was achieved at a sufficiently early age to permit appraisal. Table 2 correlates the resumption of appearance of epiphyseal centers following therapy.

7. Dr. Eldon Nickel, Dr. Earl Miller, and Dr. Donald E. Pickering are currently conducting studies relating to bone density in normal and pathological states.

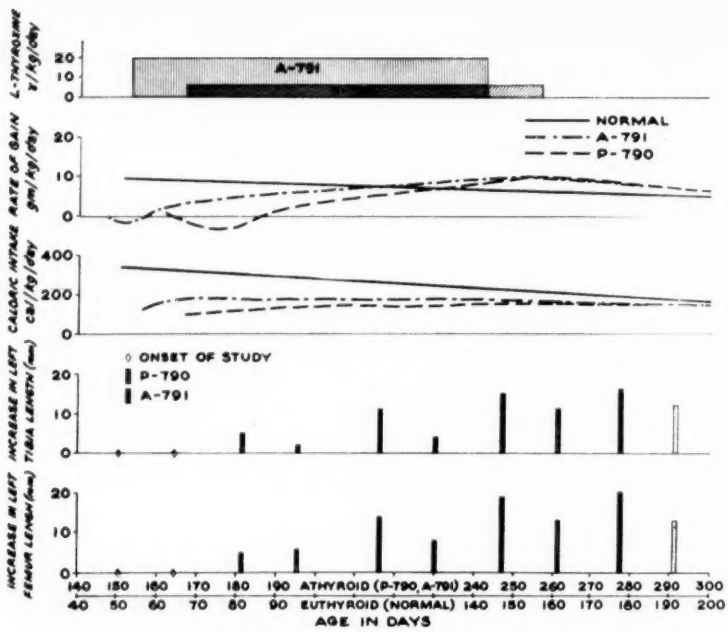


Fig. 6.—Left femur and tibia growth in treated (*l*-thyroxine) athyroid macaque infants.

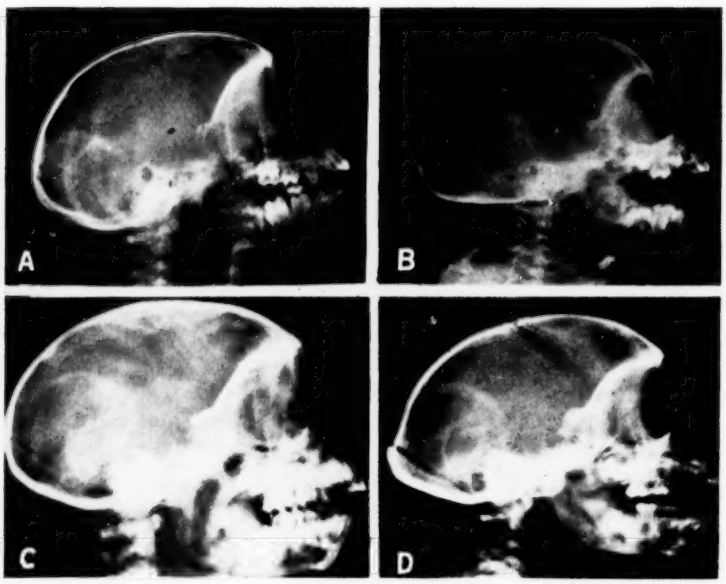


Fig. 7.—Skull films of normal and athyroid macaque monkeys. *A*, normal, age 130 days. *B*, athyroid, age 130 days (ablated age 22 days). *C*, normal, age 340 days. *D*, athyroid, age 340 days (ablated age 162 days).

Skull Development.—Significant roentgenographic changes from normal were noted in the skulls of all athyroid animals. These changes were as follows: (1) over-all growth deficit, (2) sella turcica enlargement, both relative and absolute, (3) delayed closure and widening of sutures, (4) flattening and thickening of the occipital bone and overriding of the basiocciput, and (5) delayed eruption of deciduous teeth. The most pronounced of these changes, clearly shown by 60 days following thyroid ablation, consisted of marked overriding of parietal by occipital bones, sellar enlargement, and persistent suture diastasis (Fig. 7). The reduced skull size was uniform among athyroid animals, and in the two electively sacrificed was found associated with a significantly small brain.[17] Sellar enlargement was similarly consistent and at postmorten and histopathological examination of Animals P-790 and S-775 was found to be associated with hypertrophy of the pituitary.

Measurements of the lengths of parietal and occipital bones, as found on the lateral skull roentgenograms, suggested that the overriding of the basiocciput was caused by a differential effect upon the rates of growth of these bones coincident to thyroid ablation. Specifically, delay of parietal (membranous) bone growth was greater than that of the occipital (endochondral) bone, and similar measurements during adequate therapy revealed resumption of more active parietal than occipital growth.

Eruption of deciduous teeth ceased following thyroid ablation. With institution of therapy, eruption again proceeded at a rapid rate.

In summary, long bone growth and skeletal maturation proceeded with remarkable uniformity among normal infant macaque monkeys. Thyroid ablation was followed by pronounced slowing of linear bone growth and retardation of skeletal maturation. In addition, there occurred specific skull changes. All effects noted in thyroid-ablated animals were subject to change with *l*-thyroxine therapy.

CONCLUSIONS

The role of thyroid in skeletal growth and maturation of normal and I^{131} thyroid-ablated (treated and/or untreated with *l*-thyroxine) infant rhesus monkeys was evaluated using serial (30-day) full-body roentgenograms.

Linear bone growth was constant among normal infants and between 60 and 160 days increment of tibia or femur was approximately 20 mm. Skeletal maturation among normal infants was characterized by a rapid appearance of secondary centers of ossification.

Skeletal changes induced by thyroid ablation included marked and uniform diminishing rate of linear bone growth; delayed appearance of secondary centers of ossification, and characteristic skull changes which included an over-all growth deficit, enlargement of the sella turcica, delayed closure of sutures, delayed eruption of deciduous teeth, and flattening and thickening of the occipital bone with overriding by the basiocciput.

Adequate replacement therapy (20 γ per kilogram per day of *l*-thyroxine) resulted in the resumption of a normal rate of linear bone growth, appearance of secondary centers of ossification, and developmental progression toward normal skull features. Administration of 6γ per kilogram per day reversed all effects except those in the skeleton.

COMPLETELY AUTOMATIC MILLER AEROSOL DEVICE

LIEUTENANT CHESTER M. TROSSMAN (MC), U.S.N.

RECENTLY Dr. J. B. Miller described an ingenious device for the prolonged administration of an aerosol.[1] The administration of water or a detergent solution (Alevaire[2]) as an aerosol vapor has proved an extremely effective way to liquefy tenacious secretions deep in the respiratory tract in such diseases as laryngotracheitis, interstitial pneumonitis, and atelectasis of the newborn.[3]

The purpose of this article is to describe a modified Miller apparatus which will operate indefinitely with a minimum of attention as long as supplied with fluid and compressed air or oxygen. Since the same level of fluid is maintained constantly in the nebulizer bulb, the apparatus will neither flood nor drain dry.

Dr. Miller found that a loaded De Vilbiss No. 40 nebulizer[4] would produce a strong aerosol current when a source of compressed air or oxygen was substituted for the hand bulb supplied with the nebulizer. He connected 3 ft. (91 cm.) of ½ in. (1.3 cm.) diameter flexible rubber tubing to the outlet vent of the nebulizer and inserted the free end of the tubing into whatever he wished to deliver the aerosol into, for example, incubator, oxygen tent, etc. He dripped the fluid to be nebulized into the reservoir bulb of the nebulizer via a No. 18 needle inserted through the shortened rubber stopper of the side vent. Theoretically, by dripping in fluid at the same rate at which it was being expended, one could maintain a sufficient quantity in the reservoir to keep the nebulizer going indefinitely.

In practice, however, either the inflow would be too fast and the aerosol jet would be drowned out, or the inflow would be too slow and the reservoir would drain dry. The success of the device depended on developing some way of keeping a suitable amount of fluid at a constant level in the reservoir.

The key problem of maintaining a constant fluid level in the reservoir was partly solved in the original apparatus by means of a simple siphon consisting of a Venapack plastic tubing connected at one end via a second No. 18 needle inserted through the shortened rubber stopper of the side vent and at the free end to a 1-gal. (4-liter) drainage bottle on the floor level. This simple siphon worked to drain out excess fluid from the reservoir as long as the inflow rate was about 40 drops per minute. When the rate of inflow decreased the siphon would drain the reservoir

The opinions and views set forth are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. Miller, J. B.: Apparatus for Prolonged Continuous Aerosol Administration, A. M. A. Am. J. Dis. Child. **84**:616-621, 1952.

2. Alevaire, an alkylaryl polyether alcohol detergent suitable for use with the nebulizer, is available from Winthrop-Stearns, Inc., 1450 Broadway, New York 18.

3. Ravenel, S. F.: New Technique of Humidification in Pediatrics, J. A. M. A. **151**:707-711, 1953.

4. The No. 40 nebulizer is manufactured by De Vilbiss Company, P. O. Box 552, Somerset, Pa.

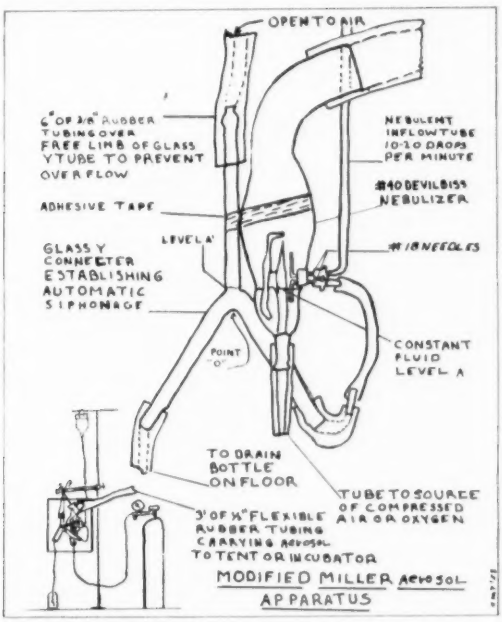

OPEN TO AIR
6" OF 3/8" RUBBER TUBING OVER FREE LIMB OF GLASS Y TUBE TO PREVENT OVER FLOW
ADHESIVE TAPE
LEVEL 'A'
GLASS Y CONNECTER ESTABLISHING AUTOMATIC SIPHONAGE
POINT "O"
NEBULENT INFLOW TUBE 10-20 DROPS PER MINUTE
#40 DEVILBISS NEBULIZER
#18 NEEDLES
CONSTANT FLUID LEVEL A
TO DRAIN BOTTLE ON FLOOR
TUBE TO SOURCE OF COMPRESSED AIR OR OXYGEN
3' OF 1/4" FLEXIBLE RUBBER TUBING CARRYING AEROSOL TO TENT OR INCUBATOR
MODIFIED MILLER AEROSOL APPARATUS

Fig. 1.—The automatic siphon operates 24 hours or longer with minimal attention.

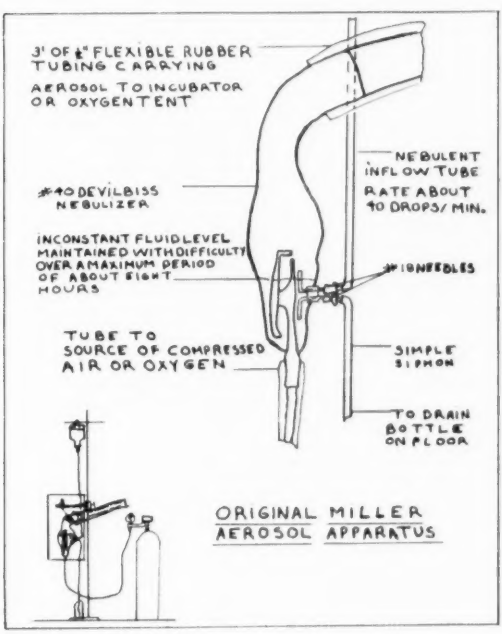

3' OF 1/4" FLEXIBLE RUBBER TUBING CARRYING AEROSOL TO INCUBATOR OR OXYGEN TENT
#40 DEVILBISS NEBULIZER
INCONSTANT FLUID LEVEL MAINTAINED WITH DIFFICULTY OVER A MAXIMUM PERIOD OF ABOUT EIGHT HOURS
TUBE TO SOURCE OF COMPRESSED AIR OR OXYGEN
NEBULENT INFLOW TUBE RATE ABOUT 40 DROPS/MIN.
#18 NEEDLES
SIMPLE SIPHON
TO DRAIN BOTTLE ON FLOOR
ORIGINAL MILLER AEROSOL APPARATUS

Fig. 2.—The simple siphon and rapid inflow of the nebulent permit continuous performance for only about eight hours. Frequent adjustment and refilling are necessary.

dry, "suck air," and cease functioning. After the siphonage was broken the reservoir bulb would simply fill up and flood over the aerosol jet unless the siphon was started again by "milking" the siphon tube. Moreover, the spihon worked so rapidly that after eight hours the clysis bottle suspended above the nebulizer would have to be reloaded and the drainage bottle on the floor emptied. Consistently good results could not be obtained even with a flow of 40 drops a minute, because as one approached that rapid rate of delivery, fluid would start to run down the sides of

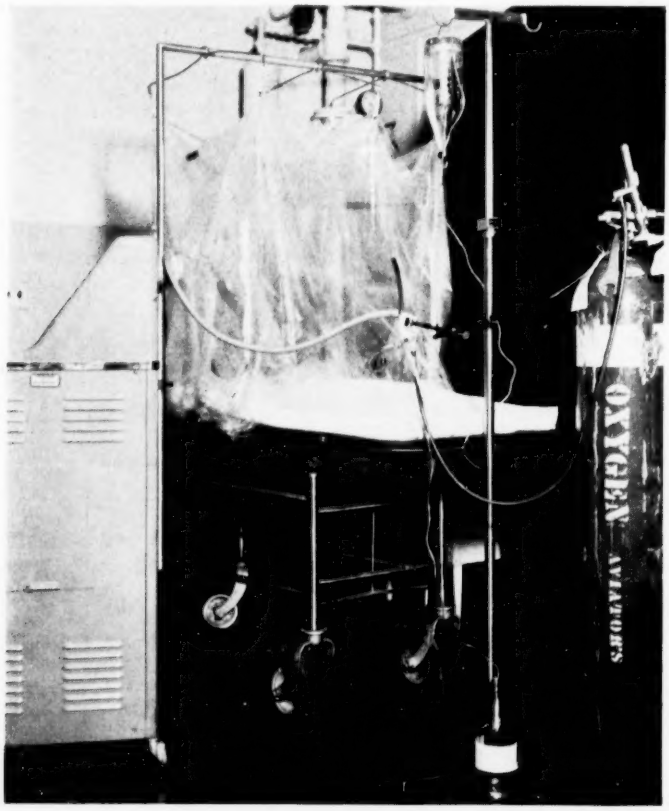


Fig. 3.—Modified Miller aerosol apparatus connected to a plastic oxygen tent by slipping the flexible rubber lead-off tubing beneath the sleeve over the intake manifold of a standard model electrically cooled oxygen tent air conditioner.

the small drip indicator of the Venapack, and the drops could not be counted. Furthermore, making fine adjustments in the rate of flow through the resilient plastic tubing was difficult.

The problem was solved by inserting a Y-glass connecter in the simple siphon as shown in Figure 1. A 6-inch (15 cm.) piece of rubber tubing was placed over the vertical free limb of the Y tube as a safety feature in case of overflow from the clysis bottle suspended over the nebulizer. Since the level of fluid in open vessels connected by a pipe will be the same, level A in the bulb moves simultaneously with level A' in the vertical limb of the Y connecter.

Fig. 4.—Close-up of the automatic siphon of the modified Miller aerosol apparatus.

When level A′ rises above point O, junction point of the three limbs of the Y connecter, the siphon is started. The levels A and A′ drop to a point just below O where air enters the system and siphonage is broken. Thus the height of level A in the bulb is determined by the location of point O in the connecter. The siphon always works to bring level A back to a position horizontal with point O. To obtain proper operation of the nebulizer, the junction of the three limbs of the Y connecter, point O, is taped to the bulb about 7/8 in. below the tips of the capillary tubes in the nebulizer. Thus the aerosol jet is never flooded, the bulb reservoir of the nebulizer is never completely emptied, and continual operation is assured. The only precaution necessary is to avoid a rate of inflow that exceeds the capacity of the system to expend fluid through nebulization and siphonage. A suitable rate of inflow is between 5 and 20 drops per minute depending on the fluid nebulized, rate of flow of air through the system, and characteristics of the nebulizer used. When the apparatus is working properly, only a few ounces of fluid will collect in the drainage bottle in 24 hours. The principles of siphonage in the original Miller device and our modification can be compared in Figures 1 and 2. Figure 3 shows a complete setup using the modified device, and Figure 4 shows a closeup of the nebulizer with our siphon attached. Such a siphon could be made of glass and be built into the apparatus in the factory. The siphonage principle involved here is the same one used in the Munro tidal-drainage apparatus.[5]

COMMENT

With the modification we have described the Miller aerosol apparatus becomes an inexpensive, dependable, flexible, and effective means of giving patients with respiratory difficulties the benefit of continuous aerosol therapy. The total cost of the apparatus is about $3. A minor improvement we made in the original apparatus was to suspend the nebulizer from the clysis stand by means of a heavy and light ring-stand clamp. These holders gave the apparatus more flexibility and prevented the bulb from smashing against the pole of the clysis stand. By keeping the nebulizer below the rubber outflow tubing and by keeping the tubing free from kinks, any condensate formed in the tubing will drain back into the bulb and be renebulized. The elimination of pooled condensate in the outflow tubing permits a freer passage of the aerosol current through the system. The Y-glass connecter and short piece of rubber tubing used to modify the apparatus are inexpensive and available at any hospital.

SUMMARY

The Miller aerosol apparatus was modified by inserting a glass Y connecter into the siphon tube of the original device. The junction point of the limbs of the Y tube was taped onto the bulb of the nebulizer. A 6-in. piece of rubber tubing was placed over the free vertical limb of the Y tube in case of overfilling of the reservoir bulb of the nebulizer. This modified apparatus will run indefinitely with a minimum of attention and provides a virtually foolproof method for prolonged administration of an aerosol to a patient with a respiratory ailment.

Captain F. K. Smith (MC), U. S. N., Medical Officer, and Commander George C. Calderwood (MC), U. S. N., Chief of the Dependents Unit, gave encouragement in the preparation of this material. Mrs. Dorothy Doane typed the manuscript.

5. Munro, D., and Hahn, J.: Tidal Drainage of Urinary Bladder, New England J. Med. **212**:229-239, 1935.

Progress in Pediatrics

NATIONAL POLICIES RELATIVE TO THE DISTRIBUTION OF GAMMA GLOBULIN

W. H. AUFRANC, M.D.
WASHINGTON, D. C.

IT IS UNUSUAL in governmental procedure for a defense mobilization agency to be concerned with the civilian distribution of a biological such as gamma globulin. This procedure came about in the following manner.

Shortly after the start of the Korean War, in 1950, there was a sudden demand for large quantities of whole blood for our combat troops. It soon became apparent also that a program of blood collections for the production of dried plasma for stockpiling should be developed. The National Security Resources Board requested the American Red Cross to assume this responsibility as it had done during World War II and, in addition, to plan for the collection of blood for a stockpile for civil defense needs.

In April, 1951, after the Defense Production Act of 1950 and the establishing of the Office of Defense Mobilization, the health resources activities of the National Security Resources Board were transferred to the Office of Defense Mobilization.

In June, 1951, the American Red Cross and the Department of Defense requested the Office of Defense Mobilization to assume the over-all responsibility for the allocation of blood to the Department of Defense and the newly created Federal Civil Defense Administration, there being but one source of blood and two claimants. The Director of the Office of Defense Mobilization appointed a subcommittee on blood to study the problem, and on Dec. 10, 1951, the President sent a letter to all federal agencies and departments requesting cooperation in the program.

The Subcommittee on Blood, through the Health Resources Advisory Committee of the Office of Defense Mobilization, developed a single national blood program concept designed to serve the total needs of the federal government without duplication within government or interference with programs to serve civilian needs. To date, the National Blood program has continued to operate with informational material being furnished to the public from one source, telling one story as to the blood needs, and the Subcommittee on Blood has continued to make allocations of plasma to the Defense Department and the Federal Civil Defense Administration.

In February, 1952, the National Foundation for Infantile Paralysis invited the Office of Defense Mobilization to review the results of its first field trials in Provo,

Director, Health Resources Staff, Office of Defense Mobilization, Executive Office of the President.

Read before the joint meeting of the Section on Pediatrics and the Section on Physical Medicine and Rehabilitation and the Section on Preventive and Industrial Medicine and Public Health at the 102nd Annual Session of the American Medical Association, New York, June 4, 1953.

Utah, in 1951, on the use of gamma globulin for the prevention of paralytic poliomyelitis. That report was promising, and it was felt that if subsequent field trials were equally promising, some steps should be considered with respect to making the best use of the expected limited supply.

Since the Office of Defense Mobilization was already engaged in the National Blood Program with the American Red Cross for the defense agency's plasma stockpiling program, and the Red Cross had already fractionated a considerable amount of gamma globulin over the past nine years, it appeared logical that the Office of Defense Mobilization should assume the initiative in trying to work out the basic policies of the type of program that might be needed.

The first step in this process was to forestall undue hysteria during the summer of 1952 until further field trials could be conducted. It was therefore decided to issue a statement to the medical profession to the effect that field studies to date were inconclusive. This was done on May 26, 1952.

Shortly after this release, the Health Resources Advisory Committee and the Subcommittee on Blood met jointly to consider the problems which would arise if the next field trials showed that gamma globulin was of definite value in the prevention of paralytic poliomyelitis. Further consultations were held with representatives of the Public Health Service, the American Medical Association, the American Red Cross, the National Foundation for Infantile Paralysis, and the state and territorial health officers. It was decided that in view of the National Research Council's penicillin-distribution experience during World War II, it should be asked to appraise the situation and advise accordingly.

On Oct. 20, 1952, Dr. William McD. Hammon, together with the National Foundation for Infantile Paralysis, advised us of the 1952 field-trial results in Houston, Texas, and Sioux City, Iowa, whereupon it became obvious that there would be an increased demand for gamma globulin as a result of these further studies.[1] Dr. Hammon's studies were conducted on a community, or mass-prophylaxis, basis among the age groups at greatest risk to the disease. In his studies in Harris County, Texas, where the epidemic rate was 82 per 100,000 population, only 0.4 cases were prevented per 1,000 injections. The effectiveness rose to 3.4 per 1,000 in the Iowa study, where the epidemic rate was nearly 400 per 100,000 population.

After a series of conferences with interested agencies, the Office of Defense Mobilization, on Nov. 21, 1952, requested the American Red Cross to assume the additional responsibility of collecting the blood necessary to meet the minimal needs of gamma globulin for 1953. On Dec. 8, 1952, the American Red Cross accepted the responsibility of collecting the additional blood necessary to make available all the gamma globulin possible for the prevention of paralytic poliomyelitis.

Since 1943, the American Red Cross had made available to the states a little over 8,000,000 cc. of gamma globulin, plus the amount used for the poliomyelitis studies and other types of clinical research.

During October, 1952, the National Research Council established an *ad hoc* committee on the uses of gamma globulin, and, together with their Subcommittee

1. The Distribution and Use of Gamma Globulin, A Statement by the Division of Medical Sciences, April 20, 1953, National Research Council.

on Shock and Subcommittee on Sterilization, as well as the Committee on Blood and Related Problems, presented recommendations on the role of gamma globulin in the prophylaxis of poliomyelitis as follows[2]:

"1. The preliminary scientific evidence presented indicates that the administration of gamma globulin has limited prophylactic value from the end of the first week through the fifth week after it has been injected. The Division reserves any further judgment pending the availability of final clinical follow-up examinations and of the results of pertinent laboratory studies.

2. From the scientific point of view, it is felt that gamma globulin does not provide a practical solution to the problem of the prevention of paralytic poliomyelitis. The most promising field of investigation definitely appears to be the development of a polyvalent vaccine.

3. From the practical point of view, while every reasonable effort should be made to provide adequate amounts of gamma globulin, as an interim measure, for minimal estimated epidemic needs for poliomyelitis in the coming season, primary consideration should be given to the requirements of the Armed Services and of Civil Defense for whole blood and its derivatives and for gamma globulin, for the prophylaxis of measles and infectious hepatitis.

4. Attention is called to the fact that present production of gamma globulin is but a small fraction of the minimal epidemic need for poliomyelitis alone, as estimated by the National Foundation for Infantile Paralysis. This fact emphasizes the urgent need to increase the rate of fractionation of human plasma as rapidly as possible."

At the suggestion of the producers of gamma globulin, the Office of Defense Mobilization sponsored a series of three industry meetings to discuss ways and means of creating a central pool of American Red Cross gamma globulin together with the commercially produced gamma globulin. It was industry's firm stand that they wanted no part of a governmental allocation authority, but preferred to distribute by the free-enterprise system and permit the American Red Cross material to be distributed under a controlled system. After this series of discussions, however, the National Foundation for Infantile Paralysis offered to buy the total production of the commercially produced gamma globulin and make this available to the Office of Defense Mobilization along with the American Red Cross material for allocation to places where it was needed most. The National Foundation for Infantile Paralysis was successful in this attempt, and on Feb. 4, 1953, the acting director of the Office of Defense Mobilization assumed the responsibility for distributing the supplies of gamma globulin made available to the Office of Defense Mobilization by the American Red Cross and the National Foundation for Infantile Paralysis or any other source.

At this point the National Research Council proceeded to develop a plan of allocation on the advice of a special panel on allocation. This plan[3] provides for a basic allocation of 3 cc. per median number of reported cases of measles over the five-year period 1947-1951 for use in measles and infectious hepatitis. No restric-

2. Role of Gamma Globulin in the Prophylaxis of Poliomyelitis, Recommendation to the Office of Defense Mobilization, Oct. 19, 1952, National Research Council.

3. Office of Defense Mobilization, Distribution of Gamma Globulin, J. A. M. A. **152**:68 (May 2) 1953.

tions were placed on the use of gamma globulin for measles and infectious hepatitis protection as indicated by the National Research Council recommendations. A basic allocation of 60 cc. per average number of cases of poliomyelitis in the period of 1947-1951 will be supplied to the states. Additional amounts on the same basis for cases above this five-year mean will be furnished. This basic and additional allotment is recommended for household and other intimate contacts of patients up to the age of 30 years in clinically diagnosed cases and for pregnant women of any age who are contacts of patients.

The recommendation is also made that gamma globulin may be used for contacts of patients in "suspect cases" in high-endemic situations. About 33% of the total supply is to be reserved in the national pool for mass prophylaxis in communities reaching a very high incidence during the year. Complete details as to when a State Health Officer may apply for gamma globulin for this purpose will soon be furnished to state health officers. An area may be eligible for this additional material when the following criteria are satisfied: at least five clinically diagnosed new cases in the county since the first of the calendar year or the low point of the previous season, whichever is later; an annual estimate of at least 20 cases for the county, and an annual estimate of at least as many clinically diagnosed cases in the county per 100,000 population as the critical poliomyelitis incidence. This shall be established as the minimal annual number of clinically diagnosed cases per 100,000 (1950) population required to balance the number of 10 cc. doses of gamma globulin for mass community prophylaxis with the number of children under 15 years of age in all counties achieving this critical incidence in 1953. The critical poliomyelitis incidence shall be calculated in accordance with the following: (1) the quantity of gamma globulin allocated for this purpose; (2) the county morbidity data through the latest reported week, extrapolated to the end of the calendar year in accordance with the seasonal pattern of incidence of poliomyelitis in the state in which the county is located. Periodic recalculations shall be made of this critical poliomyelitis incidence, to take into account changes both in the national poliomyelitis forecast and in the remaining supplies of poliomyelitis immune globulin allocated for this purpose.

An additional 10% will be held in reserve for other unforeseen emergencies or conditions.

The actual distribution of the gamma globulin has been delegated to the Public Health Service, United States Department of Health, Education, and Welfare, which will receive all requests and take action in accordance with policies established by the Office of Defense Mobilization. The State Health Officer has been given full responsibility for the distribution and method of use within his State.

During the course of the many discussions on this problem, it was stated that we were in reality dealing with a problem of potential hysteria. The value of gamma globulin in the prevention of paralytic poliomyelitis is not such as to offer hope for any material reduction of the disease in 1953, no matter how it is used. It was frequently stated that we were not justified in attempting to control use of the material except to prevent, insofar as possible, black-market activities. The Hammon field trials were on a mass-prophylaxis basis to certain age groups of children, which is the only method of proved value, but the expected amount of gamma globulin available this summer, if used entirely on this basis, would deprive many areas of

any gamma globulin at all. Multiple cases of poliomyelitis do occur in families, and it was felt that this is where the hysteria would develop and that if gamma globulin is given early, some cases may be prevented or modified. This procedure, of course, offers no hope for the protection in the first, or index, case. It is also true that many cases occur consecutively in individual families, as well as that multiple infections do occur in the same family simultaneously. It would appear that from 80 to 90% of the patients would not be offered benefit of protection by employment of the family-contact method.

However, in terms of the number of cases prevented per 1,000 injections, the household-contact method may be expected to be as effective as the community prophylaxis method and may actually be more effective if weight is given to modification as well as prevention of disease.

The supply of gamma globulin for 1953 is derived from two sources: (1) that produced from donated blood collected by the American Red Cross, and (2) that derived from placental blood, commonly referred to as commercial gamma globulin in contradistinction to the blood donated by the American people. At the present time there are six producers of gamma globulin, and for 1953 it is estimated that about 25% of the gamma globulin to be made available will be produced from placental blood and about 75% will be from donated, or Red Cross, blood.

Currently there are two products being allocated to State Health Officers, immune serum globulin and poliomyelitis immune globulin, the latter having been tested against the Lansing strain of poliomyelitis. It is our understanding that all producers are now testing their total production against the Lansing strain, so that in the future we may expect to have largely one product labeled as poliomyelitis immune globulin that will be useful against measles and infectious hepatitis as well as poliomyelitis. In addition to this somewhat confusing nomenclature situation, there will be an administrative problem to solve in connection with making allocations of one product for three diseases where there has been no restriction on its use for measles and infectious hepatitis; there should continue to be some restriction on its use for poliomyelitis. It has been estimated that of the some 40,000,000 children in the United States there will be only a little over 1,000,000 average poliomyelitis doses of gamma globulin available for use in this disease.

The allocation of gamma globulin for measles and infectious hepatitis this year has not been a particularly disturbing problem because of the relatively low incidence of measles so far. This office has placed no restriction on the use of gamma globulin for measles and infectious hepatitis and has filled all requests to date. As of June 1, a total of 633,790 cc. of gamma globulin had been requested by state health officers since Jan. 1 of this year, and this amount has in turn been furnished. This is slightly less than 50% of the amount originally estimated that would be needed for this calendar year.

On May 15, the first supply of poliomyelitis immune globulin became available for use in the United States, and as of June 1 about 700,000 cc. had been received; by this date this amount will have been distributed to the states as a part of their basic allotment. This represents about 50% of the basic amount alloted under the distribution plan.

The production outlook of poliomyelitis immune globulin for the remainder of the year is slightly better than had been originally anticipated. The original estimate was that there would be about 1,000,000 average doses (7 cc.), and it now appears that there will be about 12,000,000 cc. available instead of the original 7,000,000 cc. It should be pointed out, however, that this amount will not be available for the expected peak of the disease season.

In ending this statement regarding the national policies, I wish to emphasize that the plans developed for the distribution of gamma globulin posed a rather serious problem, and the plans that were finally adopted were developed in good faith and with early unanimous agreement that no one wanted the responsibility for the job. If the real hysteria is to be among household contacts of cases, then it should be somewhat reassuring to know that enough gamma globulin will be available during 1953 for use among household contacts of clinically diagnosed cases, barring of course an extremely high epidemic year or a tremendous amount of overreporting.

ROLE OF THE GENERAL PRACTITIONER AND SPECIALIST IN CARE OF PHYSICALLY HANDICAPPED CHILDREN

SAMUEL M. WISHIK, M.D.
PITTSBURGH

NOT EVERY person with a physical disability is handicapped by it. The definition of the term "physically handicapped child" as used in this paper is a child who, because of a physical disability, cannot compete on equal terms with other children. The mere existence of a physical deviation does not make it a disability. A child with a hammertoe or with mild weakness of a thumb subsequent to polio need not be considered handicapped.

Furthermore, physical handicaps are not limited to those which affect use of the arms or legs. A child who is deaf is just as handicapped as a child who carries a crutch. Disabilities such as heart disease or deafness are more difficult to bear because they are not obvious externally and do not receive the same consideration and attention from others.

There are still other kinds of physical handicaps with equal or greater impact on the individual. One instance is the case of a 4-year-old boy who at the age of *2* had upset a pot of hot rice on his head, with resultant loss of much of his hair (Fig. 1). Jimmy sat sullenly in a corner by himself, did not play with the other children, and in the six weeks that he had been in the shelter had not uttered a single word. The staff was not sure whether or not he was mentally deficient or possibly psychotic. A toupe was purchased and fitted for Jimmy (Fig. *2*). The pictures before and after tell the story. Almost immediately, Jimmy opened up, talked, laughed, and played. He is now an outgoing and friendly child.

In respect to the care of handicapped children, the physician naturally thinks of his most immediate roles—making a diagnosis and giving medical treatment. These constitute only a portion of the services needed by the handicapped child. The objective of medical care should not be merely to correct the disability of an arm or leg or other part of the body without consideration of the ultimate status of the individual as a well-adjusted contributing adult member of society. The complete program includes (1) prevention of disability, (*2*) early case finding, (3) diagnosis, (4) medical care, (5) education, (*6*) help in adjusting to the handicap, and (*7*) vocational aid.

In addition to making the first diagnosis and giving medical care, the physician has a role to play in respect to each one of the components of care listed. Without his participation, the best and most appropriate care for each child either cannot be given at all or is rendered less effective. In the discussion which follows, emphasis will be given to the role of the physician in each of the components of total rehabilitation.

Presented before the Medical Society of the County of Queens, Inc., N. Y., Jan. *27*, 1953.

Professor of Maternal and Child Health, Graduate School of Public Health, University of Pittsburgh School of Medicine.

1. PREVENTION OF DISABILITY

Within our present state of knowledge, many handicapping conditions are preventable. The physician can contribute toward that prevention in a number of ways, depending on the specific condition under discussion. Accidents, for example, lead all other causes of death and also cause much crippling in childhood. Home accidents take a prominent place in that unhappy story, and most home accidents could be prevented if parents were informed, alerted, and cautious, and if home equipment were properly designed, manufactured, and maintained.

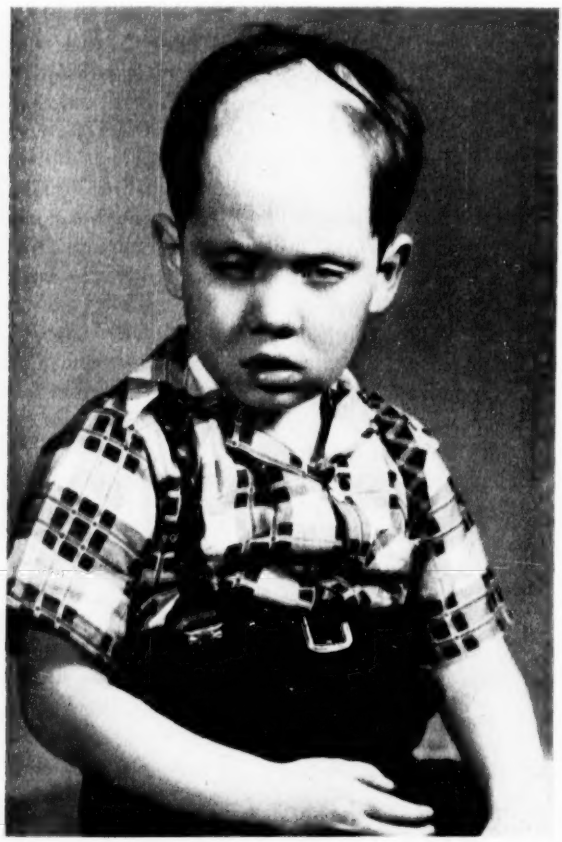


Fig. 1.—Jimmy, when first seen.

Today, a good portion of the general practitioner's and pediatrician's practice consists of supervising the health of well children and of guiding parents in child rearing. Such guidance is incomplete without helping to educate parents on home accident prevention for each age group. The physician should inform parents in advance that 9-month-old babies swallow safety pins, that 15-month-old babies aspirate nuts, that toddlers climb not only on accessible places, but push furniture around to get to seemingly inaccessible ones, that they reach up for the projecting pot handle on the stove, and that runabout preschool-age children swallow rat

poison or burn themselves with matches. Broken arms and legs, cosmetic disfigurement, amputations, and lifetime disability result from carelessness of a moment or lack of advance attention to simple safeguards.

The physician can help prevent disability from other causes than accidents. If giving of gamma globulin prevents or modifies measles after a known exposure, a case of encephalitis with resultant mental deficiency, deafness, or cerebral palsy might have been prevented. It is reasonable to believe that advice to pregnant women concerning nutrition during the prenatal period might help to prevent the occurrence of congenital malformations in the offspring. The doctor should help

Fig. 2.—Jimmy, after being fitted with a toupeé.

encourage families to seek dental care for their children early. Good care and protection of the deciduous teeth may prevent deformity of location or occlusion and resultant need for orthodontic care during adolescence.

Another important contribution of the physician to prevention is the effective treatment of conditions which, if neglected, are likely precursors of permanent disabilities. In the child with history of rheumatic fever, aggressive attention to the hazard of repeated respiratory infections and supervised administration of prophylactic medication can make the difference between a child with a normal heart and one with serious heart damage. The general practitioner or pediatrician who sees a 2½-year-old child with mild strabismus and tells the parents reassuringly that the child will outgrow it has probably cost that child his only chance to learn the function of fusion of images and to develop full coordination of eye motion.

2. EARLY CASE FINDING

Early case finding is obviously impossible if the patient does not come to the physician. Routine health examinations constitute favorable opportunities for access of patient to physician and for case finding. There are several times when routine examinations are done.

A. Examination of the Newborn Infant.—Too often, the examination of the newborn infant, both at the time of birth and at the time of discharge from the hospital, is cursory. This is the time to look carefully for certain congenital malformations or evidences of birth injury which might lead to permanent disability. Correction of club foot is easier when treatment is initiated early. Dislocated hip, either unilateral or bilateral, should be looked for. Coarctation of the aorta can easily be recognized by palpating for the femoral pulse. Even cleft palate has been missed by a too-quick look in the mouth.

B. Health Supervision of the Preschool Child.—This is the age when early deviations can be recognized by careful observation and seeking for them. This is a time when subtle differences must be sought between abnormalities and conditions which, in character or in time of development, lie toward the extremes of the normal range. In the latter, the family can be assured that the child will eventually "grow out of it," whereas the real deviations from normal will probably grow worse. For example, the suspicion of a strabismus, even though slight, should be verified by the cover test.

The question might be asked as to whether the routine periodic examination allows enough time to examine for all kinds of deviations. The answer lies in separating out the things that are looked for at different examinations. For example, the initial examination of the newborn infant or the preschool child at the first visit is comprehensive and seeks certain things which, once identified, do not have to be checked again. Once the femoral pulse is definitely felt, it is not necessary to seek for possible coarctation any time thereafter. At subsequent routine revisits, distinction should be made between the visit at which an inspection of certain items is made and the less frequent occasions at which a full periodic reexamination is done.

C. School Health Program.—Periodic screening tests done in the schools are aids to case finding. Private physicians recognize in particular the value of routine vision and hearing testing. The carefully done audiometric test is far more reliable than a whisper or watch-tick test.

D. Follow-Up of "Vulnerable" Groups.—Of at least equal importance to the finding of a disability in the process of routine observation of healthy children is the identification of certain events, illnesses, or episodes which are frequent precursors of the subsequent development of a handicap. Once identified, these patients fall into "vulnerable" groups and an individualized follow-up schedule should be set up for each one. When there is no known method of prevention, the follow-up is intended for case finding rather than prevention and for initiating the best known supervision or therapy. Obviously, small premature infants should be examined for retrolental fibroplasia. Premature infants, babies who have had Rh difficulty, and those who have been anoxic or had other difficulty during the neonatal period should be followed for evidence of brain injury such as cerebral palsy. The child who has had nonparalytic polio should be checked for a year or two for possible development

of scoliosis. Children in a family with a history of diabetes should have careful attention given to the possible development of diabetes. The baby who weighs 9 lb. (4,080 gm.) or over at birth may be a clue to a prediabetic status in the mother and, subsequently, possibly in the baby itself. The child with an attack of rheumatic fever is followed for signs of heart damage. The young child who has a nonspecific convulsion incidental to a febrile illness has a somewhat greater chance of having epilepsy than another child. A definite history of German measles in the first two months of pregnancy would warrant careful examination of the eyes, heart and other parts of the baby for congenital malformations.

3. DIAGNOSIS

Once a disability has been suspected by the general practitioner, certain logical steps should follow.

A. Intensive Examination.—The physician makes a more intensive examination with particular consideration of the matter under concern.

B. Laboratory Tests.—He obtains appropriate laboratory tests, including x-rays.

C. Consultation.—He asks for consultation with a specialist.

D. "Team Diagnosis."—He and the specialist call for "team diagnosis" when additional disciplines and professional contributions are needed. Recognizing that the components of total rehabilitation include such phases as education, vocational planning, and psychological and social adjustment, the general practitioner and the medical specialist know that their contribution does not meet the total needs of the child. Even the contributions of consultants representing the other disciplines do not always meet the situation if they are made completely separately and the several opinions are then added up. It may be necessary for the representatives of the various disciplines to consult with each other and together arrive at a common decision. "Team diagnosis" may in one instance consist of several medical specialists such as the orthopedist, neurologist, pediatrician, and otologist. In the dental field, there may, in addition to the dentist, be several specialists, such as the orthodontist and prosthodontist. But outside any one profession, it is often necessary for others such as the psychologist, educator, vocational counselor, or social worker to join the physicians on the diagnostic team. Not all handicaps by far need such team approach. Some that may are cerebral palsy, cleft palate, and, more recently, congenital heart disease. The items included in a comprehensive study of the child with cleft palate, for example, are here listed.

(1) General health, nutritional status
(2) Palate—closure, function
(3) Lip—appearance, function
(4) Nose—appearance, patency, infections
(5) Teeth—number, position, condition, occlusion
(6) Ears—hearing, infections
(7) Speech
(8) Education
(9) Vocational plans
(10) Psychological and social adjustment

Over and beyond making a diagnosis, in the team approach the consultants analyze the extent and type of involvement, appraise the total status of the child, and recommend a comprehensive plan of care.

4. MEDICAL CARE

Once diagnosis, careful evaluation, and recommendation for care by consultants have been obtained, many of the patients can be carried thereafter by the general practitioner. The general practitioner may ask for periodic return to the consultant for reappraisal. In other instances, the complexity and frequency of specialized medical care needed may be such that the general practitioner and the specialist may decide that the latter should assume direct responsibility on an on-going basis for treatment of the disabling condition, while the family physician continues to supervise the general health of the child.

Of great importance in the medical care of handicapping conditions in childhood is the element of continuity. When parents allow months or years to go by during which they fail to bring the child back to the physician, he is prevented from introducing the next steps in care that would have been appropriate to the changing age of the child. The effects of this lost time may never be overcome.

For example, an infant acquires osteomyelitis which invades one of the growth epiphyses of a lower extremity. At 4 years of age, this boy may have a difference in length of the two lower extremities of ½ in. (1.3 cm.) to 1 in. (2.5 cm.), which limits him very little. He runs around, plays baseball, and keeps up with the other fellows. By the time he is 16 years of age, there may be a discrepancy of several inches in the length of the two lower extremities. The mildly handicapped child has become a very severely handicapped adult.

The child with severe hearing impairment should start to learn lip reading early and should have a hearing aid as soon as his age and mental capacity make him ready for it. A dental malocclusion must have orthodontic correction done at a specific time in relation to the growth of the jaw. A single critical year in the life of an adolescent boy with early Perthes' disease may determine whether or not he will be permanently crippled. There follows a treatment "timetable" for cleft palate, just to illustrate how, even at birth, one can in general terms predict what services will have to be considered at certain ages in the child's growth.

(1) At birth—recognition, interpretation to family, pediatric care

(2) Infancy—surgical closure of cleft lip, health supervision

(3) Preschool years—surgical closure of cleft palate, dental care, speech training, health supervision

(4) School years—surgical or prosthetic occlusion of palate, dental care, orthodontic treatment, speech training, health supervision, vocational planning.

Similar timetables can be designed for other disabilities. The physician should establish for each handicapped child an individualized timetable indicating when critical moments in the care of that child are most likely to develop. The physician has a responsibility to help meet that schedule either through his own direct relationship with the family or, when the patient fails to return, by calling upon the assistance of health departments, visiting nurse services, registers of handicapped

children, or other devices. The visiting nurse would first attempt to send the patient back to the same physician, then to another private physician, and, failing this, would do whatever seemed best under the circumstances.

5. EDUCATION

It is desirable that a handicapped child receive his education as much like and with other children as possible. On the other hand, insofar as his disability warrants separate education by special school placement, this should be furnished him. A scale of school placements ranging from the most specialized to the regular is depicted below.

Special

Hospital or home instruction
Special school for handicapped children
Special class in a regular school
Divided program—part of day in special teaching
Individually modified program in regular class
Regular program in regular class

Regular

Finding the placement that is most appropriate to each child and is available within the school system depends upon the physician's diagnosis and recommendation. In order for the physician and the school to work together on the child's educational placement, they must use a mutually understandable terminology. It does not mean very much to the school if the doctor reports a diagnosis of "mitral insufficiency" without indicating what the child may or may not do. In turn, it means little to the physician in his effort to make a recommendation concerning the child's school activities if he is told that the school offers in their physical education classes certain kinds of activities which are not too well defined, such as "adaptive physical education." The school should not only list the kinds of activities and modifications of activities that are available, but should also describe the amount of exertion and supervision connected with each. On his part, the physician should describe the activities that the child may be permitted to carry in terms of physical demands.

In addition to clarifying the situation for the schools, the doctor has a real responsibility to the child to recommend a school placement that is best for the child rather than one that might be convenient or desired by the parents. Mothers of handicapped children often coddle them and try to obtain the physician's support for their overprotection. Children with heart murmurs of a functional nature and even those with rheumatic heart changes are frequent victims of years of excessive invalidization and resultant scarring of the personality. An epileptic child under reasonably complete anticonvulsant control who has an occasional episode certainly belongs in school with other children rather than in a special class or even, as is so often the case, at home.

Another feature that deserves emphasis is the close relationship between education and medical care in obtaining improvement. A cerebral palsied child, for example, who has difficulty in use of mental faculties and in speech will often improve in his speaking and his school work if physical therapy and occupational therapy result in better control of his muscular movements and arms and legs. At the same

time, if he is helped in his mental faculties and in his speaking, the physical therapist and orthopedist will often find that there is greater relaxation and better control of the extremities.

In addition to recognizing the intimate relationship between education and medical care, the physician at times must be ready to grant greater priority of importance to education than to medical care. The decision on medical care may sometimes be to forego it in favor of the other. For example, in the child with cleft palate, the mere mechanical closure of the palate is of less importance by far than obtaining good speech. Sometimes surgical closure of the palate may cause scarring, rigidity, shortening, and increased space between the soft palate and the posterior pharyngeal wall and may exaggerate the speech defect rather than correct it. There have been recent instances in which surgeons, working in team work with the speech therapist, the orthodontist, and the prosthodontist, have decided to open up a previously sutured palate and leave it open because better speech could be obtained with a prosthesis.

6. ADJUSTMENT

The psychological and social adjustment of a handicapped child are important from at least two points of view. One is the extent of his cooperation with the medical treatment and the other, of course, is the ultimate objective of having a well-adjusted happy contributing adult.

An example of the child's cooperation with medical care is the child's use of a prosthesis. A boy of 8 or 9 years with an amputated leg may prefer to have an unsightly looking peg-leg because he can hop fast enough to go around the bases on a home run hit. At that time, he may not accept a well-fitted limb with functioning joints, but some years later, especially during adolescence, he will ask for something that looks better. The nonmedical aspects must be considered at each stage of treatment and, if given due consideration and attention, would help the physician in his treatment.

Of equal importance is the attitude of the family toward the presence of the handicap. The impact of a handicap on a child or on his family is not proportionate to the severity of the disability. Different handicaps have different effects and, of course, different people react differently to each. There is a strong element of guilt among parents who blame themselves, for one reason or another, for the presence of the handicap in the child. If institutional care seems advisable for the child, not all parents can be given such a recommendation in the same way. Some are able to institutionalize their child, and others are not yet ready to do it.

The parents need practical help in meeting their problems. They must have clarified for them immediate objectives and long-term objectives, so that they can see an ultimate horizon at the same time that they have something that they can tackle that is immediate and seems practical. They must be given a realistic approach to the ultimate objectives in the light of the child's actual potentialities as accurately as those potentialities can be appraised. Parents ask other questions such as the following: Should they have other children; will other children have the same disability? What about the sisters and brothers and the time that the mother can give to this one handicapped child as compared with the others?

The parent has an important part to play in the treatment and education of the child. The parent has to cooperate with whatever treatment the child may receive

in the doctor's office. If the doctor is seeking for improved skill in a hand, then the parent carries through in attaining that by the everyday things that go on in the home. This is just as true of education. The parent should be helped to seek and strike a balance between supporting the treatment or education that is given by the professional person and, on the other hand, the possibility that too much parental participation may conflict with the professional services. In all these respects, the physician can be a strong supporter to the parents by giving them his interpretation and advice from time to time.

7. VOCATIONAL AID

It is of little use to a handicapped person to have the best of medical care and the finest education if, unable to get a job, he finds no place for himself in the world. This may be the result of poor vocational counseling, or it may be just that the community is not ready or broad enough in its acceptance.

Vocational aid involves a number of steps: vocational planning, training, counseling, and job placement. The physician plays a part in all of these. Again, his reports and recommendations must be made not only in terms of medical diagnosis. When he appraises physical demands of a job, the physician cannot judge by mere title alone. A stock clerk in one establishment might be a person who stamps packages, but in another firm he may be the one who carries heavy boxes up four flights of stairs.

When the physician has known a handicapped child from birth or early childhood, it is too late if he and the family wait until the child is 16 or 18 and then just help him decide which job to pick. By that time the child has already made basic decisions on whether or not to continue school and at what type of school. Often the existence of a physical disability results in an attempt by the family and the child to compensate by intellectual pursuits. Because they recognize the child's physical limitations, they turn to professional or other activities in life which require use of the mind and forget that often the mind cannot sell its product to the world without the body to take it there. By working closely with the vocational counselor, the physician can help the family and the child himself to an acceptance of realistic life plans.

In former days the family physician did more than merely give medical treatment. He was counselor and adviser as well. With increasing specialization in the medical profession and greater interest of other professions in the needs of handicapped children, the family doctor lost his former role. It is not necessary to turn the clock back to return him to that position. He can now fit in with the specialists, the teachers, the vocational counselors, and others, and from his vantage point of knowledge of the child and family lead them and the professional team toward the best possible solution of the problem.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Irvine McQuarrie, M.D., *President*

Sixty-Third Annual Meeting

Atlantic City, N. J., May 6, 7, and 8, 1953

(Continued from Page 343)

Atrial Septal Defect. Dr. Alexander S. Nadas (by invitation), Dr. Walter T. Goodale (by invitation), Dr. Abraham M. Rudolph (by invitation), and Dr. Joseph J. Braudo (by invitation), Boston.

Atrial septal defects comprise at least 15% of the congenital heart lesions in children. In view of the successful surgical closure of these defects within the past year, it seemed timely to review the diagnostic criteria and the operative results and to suggest indications for surgery.

The cases of 26 patients under 16 years of age who have been studied clinically and physiologically at the Children's Medical Center of Boston are reported.

The past history of these children is remarkable in that their heart murmur was commonly not discovered until 3 years of age or later. The majority of the patients were symptom-free, only a few exhibiting mild exertional dyspnea and congestive heart failure.

Mild cyanosis was present in two children, clubbing in none. Precordial thrill was not present in any of the uncomplicated cases. Blood pressures were normal in most patients. The characteristic auscultatory findings were as follows: (*a*) widely split second sound; (*b*) basal systolic murmur of moderate intensity; (*c*) apical systolic and diastolic murmurs of varying intensity.

The two constant radiological findings were as follows: (*a*) pulmonary vascular engorgement, and (*b*) right ventricular enlargement. The electrocardiogram revealed right bundle-branch block with or without right ventricular hypertrophy in all cases.

Cardiac catheterization revealed left-to-right shunts of considerable magnitude in all these patients. The systemic blood flow was within normal limits in every instance; the pulmonary flow was considerably increased. Systemic arteriolar resistance proved to be normal in all; pulmonary resistance was increased in only a few patients. Right and left ventricular pressures as well as atrial pressures were within the range of normal in most instances. The few patients with increased pulmonary arteriolar resistance showed varying degrees of right ventricular hypertension.

In view of the above physiological data, it seems clear that the obvious purpose in attempting to close an atrial septal defect should be to decrease the work of the right ventricle and to decrease pulmonary blood flow. From this consideration it follows that two types of cases should be considered for surgery at this time: (*a*) patients in congestive heart failure with large left-to-right shunts. One can expect—and indeed we could demonstrate—a disappearance of congestive heart failure after operative closure of the defect; (*b*) patients with cardiac enlargement and exertional dyspnea who, in spite of large left-to-right shunts, do not show clear-cut evidence of congestive heart failure. In this group of patients, the indication is not as clear-cut as in the first category. Nevertheless, it may safely be assumed that, by diminishing the right ventricular work and the pulmonary blood flow to one-third or less its original level, the life expectancy of the patient will increase considerably.

It has not been considered justifiable with our still limited experience to recommend closure of atrial septal defects in patients with only small left-to-right shunts in the presence of normal or even increased pulmonary arteriolar resistance.

Detailed preoperative and postoperative studies on our patients will be presented.

DISCUSSION

Dr. Charles H. Smith, New Brunswick, N. J.: I make bold to discuss a paper on hearts because I had a long experience with a cardiac clinic. Those of you who were born since then will not remember that I started the first children's cardiac clinic in New York, at Bellevue Hospital, in 1916, and I had close contact with it for 26 years. We also see many congenitally defective hearts in private practice still.

I want to ask a question which I have never been able to get anyone to answer. How can an interauricular septal defect produce a systolic murmur? In systole, the mitral and tricuspid valves are closed. No blood can be forced through the abnormal defect opening by ventricular systole. Where is the systolic murmur formed which is so often found with these lesions? I have never had an answer to my question.

The only one I can suggest is possible relative incompetence of some of the other valves. I notice in the x-rays shown the heart is much enlarged, as it is in most congenitally defective hearts. There may be relative incompetence of other valves, but I cannot understand how a systolic murmur can originate from the interauricular defect itself.

Dr. Nelson K. Ordway, New Orleans: I wonder how much importance Dr. Nadas attributes in his diagnostic procedures to the passage of the catheter from the right to the left atrium. Perhaps he will concede, as most of us have who have catheterized patients, that the catheter is frequently passed between the two chambers when there is no functional shunt from left to right. I don't make these comments by way of belittling these data at all.

I have assumed that an apical diastolic rumble is evidence of enlargement of the left ventricle due, if you wish, to functional mitral stenosis, with a large volume of blood flowing through a normal-sized mitral valve. The genesis of this rumble is thus presumably analogous to the genesis of the systolic murmur about which Dr. Smith queried.

Dr. Nadas assured me last year that this is heard in other situations than left ventricular enlargement, and he now demonstrates it in an extraordinary number of cases of atrial septal defect. I have heard the murmur of which he speaks. In my experience it has been more diffuse, located more toward the midline and up and down the left sternal border. I wonder whether he considers that of clinical importance.

Finally, his comments about the contraindications to operation in cases in which there is a small left-to-right shunt, with or without hypertension, lead one to speculate as to what the final course is in those defects with large left-to-right shunts. Attention was called to these problems in a paper presented yesterday, the inference being that large left-to-right shunts sooner or later may lead to secondary pulmonary vascular changes.

We think we possibly have seen this in older patients. I think in particular of one 30-year-old woman who has a large atrial septal defect with a mixed shunt at this level, but going in both directions—more, however, from right to left—so that, despite her enormous heart and her pulmonary vascular engorgement, she has a pulmonary flow of less than the systemic blood flow.

I wonder whether the sequence of events in this case was not the following: a big atrial defect and a big left-to-right shunt, secondary pulmonary hypertension, right ventricular failure, and, finally, reduction of the left-to-right shunt and emergence of or increase in a right-to-left shunt.

Whether or not pulmonary hypertension will be an indication for operative correction of this anomaly will depend upon further observation of some of these cases by Dr. Nadas and, I hope, others.

He is to be congratulated for this attempt objectively to indicate what the dynamics of this situation lead to and when operative intervention should be employed.

Dr. Forrest H. Adams, Los Angeles: I wonder if Dr. Nadas isn't really presenting data on two groups of patients, those with uncomplicated atrial septal defect and those with added pulmonary stenosis? Perhaps in going over the cases the data were so similar that they were grouped all in one. However, I feel it might be confusing to other investigators to group them all into one.

And, if all the patients are grouped into one, I am wondering whether Dr. Gross has yet attacked a patient surgically with both conditions, and, if he has, which lesion did he repair first?

DR. ALEXANDER S. NADAS, Boston: I should like to thank the discussers for their comments. If Dr. Smith, in his long career, was not able to find an explanation for the second left interspace systolic murmurs, I don't know that I am qualified to try to do that.

I am just going to quote what my elders tell me. They tell me that it is caused by the relative pulmonic stenosis which, in turn, is caused by the rather large flow through a pulmonic valve that was not built to accommodate that size flow. I have to say that I don't believe this for a minute, but that is the conventional explanation.

Dr. Ordway had three questions. As to his first comment, saying that the passage of the catheter through a foramen ovale may simulate the passage of a catheter through an atrial septal defect—all the patients in this group, in which we went from right to left atrium, had a sizable left-to-right shunt. Under ordinary circumstances, the foramen ovale allows blood flow only from right to left. If the foramen ovale is so big that it will allow shunting of blood from left to right, then I think it ought to be considered to be an atrial defect and should be closed whether it originally has been a foramen ovale or not.

About murmurs, we may not be hearing the right thing, but we certainly do hear them in patients with atrial septal defect and patients with atrial septal defect who do not have mitral stenosis either by autopsy or catheter findings.

I again have no very good explanation for it except to say that it may originate from the passage of the blood through a diaphragm-like atrial defect or possibly through a stenotic stricuspid valve. That the diastolic murmur which is toward the apex may perhaps be a little bit more toward the sternum than the classic apical diastolic murmur of mitral stenosis is possible, but we certainly think it is the same phenomenon as the diastolic murmur we hear in a patient with patent ductus arteriosus.

Finally, Dr. Ordway's last remark was about small shunts and pulmonary arterial hypertension and whether they deserve closing. I have a feeling that at the time when the shunt is small, even assuming that a large shunt had been present originally, causing the development of pulmonary hypertension, we are faced with the horse out of the barn, or the car out of the garage, whichever way you want to put it. If we are closing an atrial defect at that particular point, we may close a rather useful safety valve which may be needed as the right ventricular pressure is building up. At any rate, operation on a patient such as this was tried, and the patient died on the table. Since then, we are a little scared of it.

Finally, there is Dr. Adams' comment about pulmonary stenosis with atrial defect. Dr. Rudolph, who participated in the compilation of these data, tried to persuade me not to include pulmonary stenosis with atrial defect. We have included it because we do think that if such a situation arises, closure of the atrial defect probably ought still be attempted, because we feel if you can reduce the right ventricular flow, then the pulmonary stenosis will probably become less, since the blood offered the pulmonary valve will be less than it has been at the time the shunt was present.

Such a patient was also operated upon and died several days postoperatively in cardiac arrhythmia. Nevertheless, we feel that these patients ought to be operated on if possible. This was the reason why this clinically slightly different group has been included in our study.

The Problem of Differential Diagnosis in Infants with Large Hearts and Increased Blood Flow to the Lungs. DR. ALTON GOLDBLOOM, DR. CHARLOTTE FERENCZ, and DR. ARNOLD L. JOHNSON, Montreal, Canada.

This paper deals with the well-recognized difficulty in establishing an accurate diagnosis in infants who have enlargement of the heart associated with increased blood flow to the lungs and in whom cyanosis is not a prominent feature, although some oxygen unsaturation is common. Some patients with these findings have a patent ductus arteriosus in the absence of the typical continuous murmur. An accurate diagnosis of this condition can be made by aortography or heart catheterization and gratifying results obtained by surgical therapy. Therefore, differential diagnosis in this group is of great practical importance.

This study is concerned with 25 infants. In 19 the diagnosis was established at autopsy and in 6 by special study. The variety of the malformations which were found was striking and is one of the main factors making for the difficulties of diagnosis. The distribution was as follows:

Patent ductus arteriosus	8
With ventricular septal defect	3
With mitral stenosis	2
With coarctation of aorta	1
Anomalous pulmonary venous return	5
Ventricular septal defect with overriding aorta	4
Additional defects	2
Ventricular septal defect	4
Ventricular and atrial septal defect	2
Common atrioventricular ostium	1
Functional single ventricle	1

It is noted that there was no case of truncus arteriosus or aortic septal defect in this series.

The history and physical findings were, in many respects, similar. Repeated pulmonary infections and heart failure were common. A harsh systolic murmur at the left sternal border and an apical diastolic rumble were frequently heard. The latter murmur was associated with mitral stenosis in only one case.

The fluoroscopic examination, apart from revealing the increased vascular markings and a large heart, was usually disappointing in establishing differential points, except, perhaps, in the case of the anomalies of the pulmonary venous return, where the right atrium appeared unusually prominent.

Electrocardiography may be one of the most important aids in the analysis of an individual case. There was close correlation between electrocardiographic and postmortem findings. It is of importance that of the seven patients with patent ductus arteriosus, five showed either normal findings on electrocardiogram or a pattern of combined ventricular hypertrophy. However, in the two cases complicated by a ventricular septal defect, a pattern of right ventricular hypertrophy was present. It is noted that in the 18 cases with other diagnoses two patients had normal tracings. The details of the electrocardiograms are discussed further.

In adition to the proved cases, reference is made to a group of seven infants on whom an aortogram was made and the possibility of a patent ductus eliminated. An analysis of all the above cases suggests that there are a few criteria which make the presence of a ductus likely and a few which render it impossible. The diagnosis of patent ductus in this group could not have been made with certainty without special investigation.

DISCUSSION

DR. CHARLES H. SMITH, New Brunswick, N. J.: May I contribute a few more "quibbles"? The first thing is the fact that many newborn infants do not show congenital heart murmurs which are present later. I have been surprised many times by children who were not cyanotic and who had some dyspnea and were not normal for several weeks or months, yet in whom no murmur could be heard early.

The second point is the late development of the diastolic element in patent ductus, first called to my attention by Maude Abbott. It was somewhat of a surprise, I must confess, but watching through the years I have seen a great many ductus cases in which the patients had systolic murmurs only until they became 7, 8, or 9 years old, when the continuous murmur made the diagnosis obvious.

The third point is the character of the second heart sounds. In Dr. Goldbloom's abstract he said little about the second sounds. It seems to me they are of great importance in differentiating certain conditions. Certainly, I have never seen a ductus patent that did not have a pulmonic-second-sound accentuation.

In cases in which one suspects a pulmonic stenosis, the diagnosis is supported by a feeble pulmonic second sound. There is usually a normal pulmonic second sound in the ventricular septal defect, unless it is of very large size.

I think the second sounds are therefore of great importance.

DR. HELEN B. TAUSSIG, Baltimore: I should like to ask two questions. First, and I don't believe it was mentioned in the paper, concerning the strength of iodopyracet (Diodrast), 33%

or 35%, and not 70%, as for angiography. I just want to know if that is correct, because we feel very strongly that 70% iodopyracet is dangerous, and 35% in infants is safe for aortograms.

The other question which we have all been interested in concerns the infants with large hearts and the lack of a continuous murmur, in whom one questions the existence of a patent ductus. We have seen many patients with a patent ductus who have not had a continuous murmur until 6 or 7 years of age, some of whom would have been greatly benefited if the diagnosis had been made earlier. We are, however, only considering those children who are in difficulty. If they have a big heart and increased flow and still are doing well, there is no necessity to make diagnoses early, and we can let those children wait until a later age.

Dr. Forrest H. Adams, Los Angeles: It might be interesting at this point to recall a study made at Los Angeles County Hospital a few years back. The postmortem data on patients of all ages dying of congenital heart disease at that hospital was reviewed. In this series over 50% of the cases in which the patients died with congenital heart disease occurred under 2 years of age. Thus, I think, it can be suggested from this study that if we are to make progress in the field of congenital heart disease in the future, it is going to have to be made in this infancy period. Accordingly, I think, general pediatricians will want to refer children under 2 years of age who have congenital heart disease and who appear to be doing poorly, as Dr. Taussig has said, for more special studies.

We have had an opportunity to study 16 children under 18 months of age in whom it was eventually proved that they had a patent ductus arteriosus. All these children were operated upon surgically, and there was only one death in this group. Thus it can be seen that even small infants can be operated upon with a relatively low mortality rate with this particular lesion.

I should like to ask Dr. Goldbloom a question concerning the growth of the patients he studied with patent ductus arteriosus. Were these patients followed both before and after surgery on the same type of growth charts, and if so did their growth return to the normal channels?

Dr. Charlotte Ferencz, Montreal, Canada: I should like to thank all those who have discussed the paper and have contributed to elucidating some of the points in a rather difficult problem.

With regard to Dr. Smith's question, there was in this series one patient who showed no murmur when we first saw him at 19 days of age, and this was the patient with the functional single ventricle who was in congestive failure but was improved by digitalis. After he improved, a systolic murmur was heard. All the other patients had murmurs at any time they were examined.

The pulmonic second sound was considered accentuated in 14 of the 25 patients. In the remaining patients, it was often not mentioned in the histories. These cases were selected to a large extent from autopsy material, and many of the histories did not give information on the second sound.

With regard to Dr. Taussig's question, we have used 35% iodopyracet for all these aortograms, in a dose of 5 to 10 cc., depending on the size of the child. We have investigated only patients whom we considered to be in difficulty and thought needed operation early. We feel, however, that we have subjected some patients to special procedures for whom a diagnosis of patent ductus was, in retrospect, very unlikely, and we undertook the analysis of differential features which we presented in order to improve our selection of patients for special study.

Three patients in this series were catheterized, one with partial anomalous return of pulmonary veins and two with a ventricular septal defect.

With regard to Dr. Adams' question, there were five patients who were successfully operated on for patent ductus arteriosus. Three showed a very satisfactory spurt of growth in both height and weight. One infant, believed to have an associated mitral stenosis, is doing only moderately well, and one was operated upon too recently to evaluate the improvement gained.

The other patients with patent ductus were not operated upon. They represent cases selected from autopsy material.

Another thing I should like to add is that there was a very high percentage of associated malformations even in those patients in whom a patent ductus was found, and this is one of the factors which makes selection of patients even more difficult. Dr. Taussig, prior to the meeting, mentioned a patient she recently saw in whom a positive aortogram was obtained but who also had a functional single ventricle, so that ligation of the ductus was not helpful. In recommending patients for surgery, it must be borne in mind that the ductus may not represent the major defect.

Spectrophotometric Absorption Patterns in Erythroblastosis Fetalis. Dr. Neva M. Abelson (by invitation) and Dr. Thomas R. Boggs Jr. (by invitation), Philadelphia.

Plasmas from normal infants and from infants with erythroblastosis fetalis were examined with the Beckman spectrophotometer. Spectrums of samples obtained from diseased babies showed absorption peaks in the regions of 410 to 415 mμ, 460 to 470 mμ, and, in some cases, 620 to 625 mμ. Plasmas from normal infants showed similar peaks, but with much less absorption and with different ratios. The clinical course of erythroblastosis fetalis in many cases could be correlated with the type of absorption curve obtained. Examination of patterns before and after exchange transfusion could be performed rapidly and proved a valuable guide to treatment. The probable identity and significance of the pigments will be discussed.

DISCUSSION

Dr. Carl H. Smith, New York: Dr. Abelson has demonstrated very effectively that the serum of normal and erythroblastotic infants can be differentiated by their respective absorption curves. I would like to ask whether among the pigmentary components responsible for these changes is found methemalbumin, the compound described by Fairley to be present in the plasma of hemolytic conditions.

Dr. Wolf W. Zuelzer, Detroit: This may prove to be a very important contribution to the clinical management of erythroblastosis. All of us are unhappy about the need for correlating exchange transfusion with the bilirubin level. We have all had individual experiences with the total height of bilirubin level which proved to be misleading.

It seems to me that this offers a very promising method to look for a missing factor with which bilirubin may be very roughly correlated, but which stands in direct correlation to the fundamental disease processes responsible for the serious effects of the disease. I hope that by extending these studies to all cases of jaundice among the newborn, Dr. Abelson will find an answer to this problem. I think it is a very beautiful piece of work.

Dr. William J. Waters, Syracuse, N. Y.: I was extremely happy to see these curves as demonstrated in the peripheral blood, since we presented material before the Society for Pediatric Research this past Tuesday showing identical patterns. We believe the peak at 410 mμ to be hemoglobin and the peak at 460 mμ to be bilirubin. At the same time, we demonstrated curves from the extracts of the brain pigment from four patients with hemolytic disease of the newborn, and in each instance the maximum absorption was at 460 mμ, and therefore we believe this pigment staining the brain is bilirubin.

I wonder if the difference in the types of curves obtained by Dr. Abelson is not related to the clinical status of the patient at the time the blood sample is being examined. In the hydrops patients, for instance, the main peak, as I saw it on the chart, was in hemoglobin, and in a severe case one would expect early rapid hemolysis with freeing of hemoglobin and a high peak in the latter instance at 410mμ and, as we saw, a very small peak in the region of bilirubin, as hydropic babies are not particularly jaundiced and do not have high bilirubin levels. I don't think, however, these curves need necessarily correlate with the red blood cell counts, since the latter will be dependent on the rate of destruction as well as the rate of production.

We have found that with clinical progression of a given case, one expects a higher amount in the region of bilirubin, namely, 460mμ, and that if hemolysis does not continue, the hemoglobin peak drops out of the absorption spectra.

One other question that I would like to ask Dr. Abelson is, I wonder if in the extractions of any of these blood sera she has attempted to crystallize the pigment out by the method that Dr. Najjar has described, as we were able to get crystals from an extract of the pigmented brain areas. Also, I wonder whether she has done spectrophotometric curves on these crystals.

Dr. Edward L. Pratt, New York: As a nonhematologist, I found this a very interesting paper, because last week we had a patient who had ingested some moth balls and had acute hemolytic anemia. I was in the laboratory, and I saw this black-looking serum, and I wondered what it was; I ran it through the spectrophotometer and got curves like Dr. Abel-

son presented, although I didn't know what I was doing. The urine came out the same color and had the same absorption as the serum. It might be easier to study the pigment in the urine than in the serum.

The only comment I want to make about this is that this patient had apparently much higher levels of material in the serum and yet seemed to suffer no particular disadvantages. The material was gone over by the toxicologists, and it was found that this color was not due to napthalene derivatives.

Dr. A. Ashley Weech, Cincinnati: I just want to ask a very simple question. I wonder if Dr. Abelson happened to add a drop of sodium cyanide solution to the serum to see what happened to the absorption band.

Dr. David Yi-Yung Hsia, Boston: I should like to compliment Dr. Abelson on an extremely beautiful piece of work which has strengthened the impression which we have always had, namely, that perhaps the primary mechanism of kernicterus in erythroblastosis is not limited to that of bilirubin alone, but perhaps is also due to some pigments which are very closely related to bilirubin but which, until now, could be measured only through serum bilirubin.

I want to ask Dr. Abelson if she has succeeded in crystallizing indirect bilirubin by the method of Najjar from babies with erythroblastosis or other forms of hemolytic anemia and when it was resuspended been able to determine if this 410mμ peak was still present. Also, in what way do bilirubin and hemoglobin interfere with the 410mμ peak?

Dr. Neva M. Abelson, Philadelphia: In answer to the first question, we believe the peak between 620 mμ and 625 mμ probably represents methemalbumin (ferrihemalbumin). This has been described in other hemolytic diseases. We are not at all sure that the peak at 410mμ represents any one chemical entity, and, as I stated, it seems likely that it represents a summation of heme pigments.

I wish to thank Dr. Zuelzer for his kind remarks and to say that some of our work received an impetus from seeing the same type of case as he described. We found ourselves doing a fourth exchange transfusion on a baby whose serum bilirubin was reported as 44 mg. per 100 ml., yet the infant looked clinically quite well.

In answer to Dr. Walters, there certainly must be a relationship between time of observation and what we see at 410mμ and 460mμ. Indeed, the charts showing the courses of the babies illustrate this point. However, we do not yet have enough cases to make us feel justified in classifying them according to time of observation.

In answer to Dr. Walter's second question, I think we must remember that there are at least three factors which must be taken into account in explaining the 410 pigment: the rate of hemolysis, the character of the pigment (which may not be metabolized easily), and the infant's ability to form bilirubin.

In answer to the next question, we have also seen cases of acute hemolytic disease other than erythroblastosis fetalis in which the 410 pigment was very high. The older children did very well, but the newborn babies in our experience died. However, we must be careful in comparing cases until we are sure that the pigments are comparable.

Dr. Weech has again asked an important and stimulating question. We have not yet attempted chemically to alter the serums. We agree that chemical conversions are necessary before pigments can be identified, and of course that is probably the next step.

We have not, Dr. Hsia, crystallized the bilirubin; I think that also answers Dr. Walter's third question. We hope to leave that to the biochemists.

The Significance of Visible Iron in Red Cell Precursors. Dr. Eugene Kaplan (by invitation), Dr. Wolf W. Zuelzer (by invitation), Detroit, and Dr. Claude Mouriquand (by invitation), Lyons, France.

The presence of stainable nonhemoglobin iron in red blood cell precursors of the bone marrow provided a method for the study in vivo and in vitro of iron metabolism in relation to hemoglobin synthesis. Iron was demonstrated by means of the Prussian-blue reaction in bone-marrow films from 150 infants and children. With this technique, iron was visible in the form of discrete granules in the cytoplasm of hemoglobin-containing normoblasts. We propose the term siderocblast for normoblasts with iron inclusions.

In nonanemic subjects, at least 20% and up to 80% of the normoblasts were found to contain iron granules, as a rule limited to few small inclusions. In anemias of the type usually associated with erythroid hypoplasia (renal disease, infection, aplastic anemia) the incidence of iron-containing normoblasts and the number of granules within the cells was similar to those of the control group. In various hemolytic anemias (erythroblastosis fetalis, sickle-cell anemia, congenital spherocytosis, etc.) the number of sideroblasts was likewise within the range of the controls, but most of the cells contained multiple and larger granules. Even more prominent siderotic inclusions were found in untreated megaloblastic anemia.

By contrast, iron granules were consistently and markedly decreased in 60 cases of hypochromic microcytic anemia due to iron deficiency. On the other hand, in thalassemia, likewise a hypochromic microcytic anemia, the sideroblasts were, on the contrary, very numerous. These findings confirm the view that totally different mechanisms are responsible for the production of hemoglobin-deficient red blood cells in these two superficially similar hypochromic anemias. In iron deficiency, lack of available intracellular iron appears to be the limiting factor, whereas in thalassemia, the presence of abundant iron in red blood cell precursors indicates an intracellular block to hemoglobin synthesis. While the nature of such a congenital block remains unknown, it is possible that the problem may be illuminated by our findings in the acquired anemia associated with a known toxic agent, lead. Here, too, abundant iron granules were seen in normoblasts, although the erythrocytes were hypochromic. Both in thalassemia and in lead poisoning the normoblasts are evidently capable of taking up iron but incapable of adequate hemoglobin synthesis.

The consistent decrease of iron granules in true iron-deficiency anemia suggested the usefulness of this simple method in the study of iron deficiency. Good parallelism was observed between sideroblasts and serum iron levels. A prompt rise to normal values of sideroblasts occurred following intravenous iron therapy in six cases. Bone-marrow cultures from children with iron-deficiency anemia, grown in their own serum, showed a marked rise in iron granules when iron was added to the medium.

The data indicate that the formation of stainable aggregates of iron in normoblasts is a normal phase of iron metabolism. Their presence appears to be a prerequisite for hemoglobin synthesis, probably by furnishing an intracellular reservoir of iron. It does not in itself assure adequate hemoglobinization of red blood cells. This function depends on additional cellular mechanisms, as shown by failure of hemoglobin synthesis in the presence of abundant iron.

Iron granules in normoblasts are a highly sensitive index of the availability of iron, permit the direct visualization of a phase of iron metabolism, and provide a useful method for the in vivo and in vitro study of iron metabolism.

DISCUSSION

Dr. Carl H. Smith, New York: This paper is a timely one, since the many facets of iron metabolism are undergoing exhaustive scrutiny. Siderocytes, referring to red blood cells in circulating blood containing granules stained by Prussian blue, were studied by Macallum and Ehrlich many years ago.

The recent studies by Rath and Finch and by Hutchinson on stainable, nonhematin iron have again focused interest on the quantitive aspects of hemosiderin in bone marrow as an index of iron storage. It was pointed out by them that this simple staining reaction serves as a means for visualizing gradations in iron storage in various blood disorders and as a guide for iron therapy.

Dr. Kaplan has demonstrated graphically that what had been described for bone-marrow aspirates in general could be applied more specifically to the siderotic inclusions in normoblasts and that these were correlated with abnormalities in iron metabolism. Thus, in true iron-deficiency anemia accompanied by a low serum iron there existed meager deposits of iron in normoblasts, whereas in conditions with an elevated serum iron, such as the hereditary hemolytic anemias, lead poisoning, aplastic anemia, and cirrhosis of the liver, there was an increased amount of iron-staining material. These studies throw light on situations in which there is a need for iron as well as the detection of states with increased iron stores when iron administration is unnecessary.

I should like to know whether the structures in the vicinity of the normoblasts reflect the same quantitative picture of iron storage as in the nucleated red blood cells. In Mediterranean anemia there is always the problem of distinguishing between iron derived from multiple transfusions and that accumulated from blocked hemoglobin synthesis. It would be of interest to determine the amounts of iron present in normoblasts in cases of severe Mediterranean anemia before any transfusions are given. Do these studies in any way clarify the vexing problem of differentiating between the hemosiderosis and hemochromatosis?

Dr. Kaplan and his co-workers are to be commended for their outstanding contribution to the literature on iron metabolism.

DR. EUGENE KAPLAN, Detroit: I want to thank Dr. Smith for his very kind remarks. Concerning the questions, the extracellular iron you speak of was not demonstrable in the bone-marrow films that we prepared. Dr. Finch and the others that have used stainable hemosiderocytes as a measure of iron in storage agree that they must have particles, and in our specimens, in fact, very little extracellular iron was visible.

Concerning thalassemic patients, two of our patients were infants who had not been given transfusions, and the others were older children with multiple transfusions.

We have no knowledge concerning the applicability of this distinguishing between hemochromatosis and hemosiderosis.

Studies on Erythroblastosis Due to ABO Incompatibility. DR. DAVID YI-YUNG HSIA (by invitation), DR. ALAN RICHARDSON JONES (by invitation), DR. FRED H. ALLEN JR., (by invitation), DR. SYDNEY S. GELLIS, and DR. LOUIS K. DIAMOND, Boston.

The clinical and laboratory data on 21 infants with erythroblastosis fetalis due to ABO incompatibility are analyzed in an attempt to better elucidate the disease entity. It was found that (1) jaundice in the first 36 hours of life, (2) elevation of indirect bilirubin above physiological levels in the first three days of life, (3) negative direct antiglobulin test by the usual technique, (4) positive two-stage antiglobulin reaction, (5) high anti-A or anti-B titer in the mother after partial neutralization with Witebsky substance, and (6) elevation of both osmotic and mechanical red blood cell fragility are helpful in establishing the diagnosis. Although all of these abnormalities were not always present, they were shown to be helpful in establishing the diagnosis.

In a controlled study over a six-month period on a newborn service, 11 of the 12 infants reported as jaundiced in the first 36 hours were found to have erythroblastosis due to ABO incompatibility. The remaining one had a normal bilirubin value and was found to have no blood-group incompatibility. There were seven infants seen with erythroblastosis due to Rh incompatibility during the same study period.

DISCUSSION

DR. ROLAND B. SCOTT, Washington, D. C.: I am particularly interested in this paper because in our hospital erythroblastosis due to ABO incompatibility is five to six times as common as hemolytic disease due to the Rh factor. This, of course, is due to the ethnic composition of the population which our hospital serves.

Dr. Hsia mentioned that this syndrome is much milder than the Rh factor disease. It also seems to be much more variable. Our series is quite small, but I have been impressed by the fact that these babies might range all the way from those who need no transfusions to those who need exchange transfusions and even to those in whom kernicterus develops.

For those of us who are not hematologists, I should appreciate it if Dr. Hsia would tell us why the Coombs test is usually negative in this disease, but practically always positive in Rh factor disease. I should also like to know from Dr. Hsia how many of the mothers in his series were Rh positive. Halbrecht, who reported one of the early series of this type of hemolytic disease in the newborn, observed that this disease occurred predominantly in infants born of Rh-positive mothers. This would seem to explain why we see more of it in our hospital, because statistically our mothers (Negro) range all the way from 90 to 95% Rh positive.

I am also interested to know whether he has any data on what has happened in subsequent pregnancies in the families under study, because it is our impression that this disease is so variable that a mother may give birth to a first child with ABO incompatibility, and subsequent pregnancies may result in perfectly normal infants, although the genetic setup is the same in all. This, of course, is in contrast to Rh-factor disease where the prognosis is likely to be more unfavorable with subsequent pregnancies.

DR. WOLF W. ZUELZER, Detroit: Anyone who has dabbled in the same field will sympathize with the amount of work required in this study. As you heard, there is no one single test diagnostic of the disease.

I should like to pose the question a little differently. I wonder if one should not define the word "erythroblastosis" or the term "disease" a little more carefully. When is the presence of jaundice significant? Even when a hemolytic process is indicated by some degree of reticulocytosis, it does not necessarily constitute "disease."

At the present time, the public at large is very much alarmed about jaundice. It behooves us to investigate these situations with the greatest possible expediency. But to make the diagnosis or speak of disease is a difficult thing when the criteria are still so poorly established as they are at the present time.

Now, this problem of ABO erythroblastosis has interested us for some years because of the correlation with kernicterus, which we suspected, and which has been borne out and found by others. We made a study of a normal control group utilizing the techniques that Dr. Hsia mentioned and some additional ones. One comes up against rather startling factors.

The evidence is quite conclusive from running parallel titers between the maternal antibody against A and the fetal antibody against A that all babies who are O, that is, who are compatible, have a titer running parallel to that of the mother. Very few normal babies who are of blood group A show an anti-A titer. They do show an anti-B titer.

If you take babies in blood group B, the anti-B titer has dropped out, and the anti-A titer is sitll present. I don't know any other way to say it than to say that the baby always absorbs the homologous antibody. The question then is, why are some babies more susceptible and some babies less susceptible? These are factors about which we apparently understand nothing at all.

One little clue which has impressed itself on us is that apparently only babies who later on turn out to be blood group A_1, or right at birth are blood group A_1, seem to get the "disease," so that one may get some help diagnostically from the typing of blood group A_1.

In our experience, and I think in everyone's experience, the direct Coombs test has been occasionally positive. One has to read one's Coombs test very very carefully, and I know that that is being done certainly in the laboratory from which these studies were reported. I just want to point out that every now and then a positive Coombs test seems to go with what we call ABO erythroblastosis, so that it does not in itself indicate any very special antibody.

We found in comparison that perhaps the highest correlation with what we think is clinically significant ABO erythroblastosis is the appearance of spherocytosis as has been mentioned and the presence of antibody demonstrable by the indirect Coombs test against A_1 and not against A_2 cells in the babies' plasma.

As far as the question of severity is concerned, which Dr. Scott also touched on, that is a very difficult question. I would still plead to reserve judgment on the question as to whether there should be an exchange in any baby with this condition when the bilirubin level rises above 20 mg. We have had some experiences, as mentioned, with the appearance of kernicterus, but I don't know yet how closely we can correlate them. In most instances, we have not exchanged and have gotten by. Usually, it is a mild disease, and perhaps the studies that Dr. Ableson presented earlier will give us some clue here as to when exchange is indicated.

DR. MILTON RAPOPORT, Philadelphia: I probably have no right to say anything at this point. It is a field I know very little about. About two years ago we had an opportunity to study an ABO incompatibility in a group in whom it was artificially induced. At that times, Dr. Stokes and a group of people working with him had given 60 cc. of whole blood from parent to child to 1,800 children during the course of a poliomyelitis epidemic in Philadelphia, and fewer than 60—I think 55—of the children got a reaction at the site of injection of the blood; this was perfectly typical and practically the same in each one of the children who had the reaction.

About 10 days after the blood was given, there suddenly appeared a huge red swelling at the site of injection; it was red, painful, and attended by the appearance of fever, and we thought in the beginning it was going on to suppurate; however, it in no instance suppurated, and it completely disappeared. I studied more than half of these children, and in every one of the instances there was ABO incompatibility between parent and child; I then had enough nerve to bring back two of the children and give them injections of compatible blood. Nothing happened, and when they were given the incompatible blood, whether it came from their parent or another donor, within a matter of hours the same reaction was reproduced. Our theory was then that we had artificially stimulated the production of the type-specific agglutinin and that the ease of reproduction was obviously dependent on the persistence of a high titer. And in the cross agglutination at that time, I knew very little about any serological techniques to apply. These were crudely done, and our impression was that there were high titers of the type-specific antibodies substances in the sera of the children in whom the reaction developed.

Dr. David Yi-Yung Hsia, Boston: I want to thank the various discussers. I want to thank Dr. Scott for his remarks. I am not entirely surprised that in his population group ABO incompatibility is much more common than that due to Rh. I think the low incidence of Rh incompatibility has also been reported from such areas as New Orleans. Like Dr. Scott, we have also encountered the disease with various degrees of severity. It appears to be a characteristic of the disease.

We ourselves have not in recent times seen a case of real kernicterus due to ABO, but I have had the opportunity of seeing several in other cities where they were quite well authenticated, and these correlated with very high bilirubin levels.

As to why the Coombs test is negative, that is a classic question in this problem, which many people have worked on, but which nobody has found a very satisfactory solution for.

Dr. Jones, who created the Jones test which we discussed, has suggested that the answer must be sought on the basis of possible differences between adult and fetal erythrocytes, and in this respect the well recognized possibility of an A or B substance in the fetal cells constitutes the most striking difference.

In answer to the question of Rh-negative mothers, there were two such mothers in this group, but none of them were sensitized.

As to subsequent pregnancies, as a rule I get the impression that about 50% of mothers with ABO erythroblastosis have subsequent ABO-erythroblastic infants. This is purely a speculative impression and is not based on any figures. I have seen, for instance, one family where three successive pregnancies resulted in babies with ABO erythroblastosis, all of them with about equal degrees of severity. I have also seen families with erythroblastosis due to ABO incompatibility in which subsequent pregnancies were not sensitized.

I think we will agree with Dr. Zuelzer that it is unfair perhaps to call some of these very mild cases disease. I think that much more work needs to be done in defining what is disease and what in this disease process we should call pathological and what we should call normal.

We ourselves have not seen positive direct Coombs' tests in these babies. However, it has been reported in the literature, and there are several examples noted in Mollison's book on blood transfusions.

The severity of the disease and the criteria for treatment we are still not clear on. We have arbitrarily set a 20 mg. per 100 cc. bilirubin level because we have had so little experience in the problem, and we are very anxious to know if anyone else has had more experience with this type of problem.

The observations of Dr. Rapoport are very interesting, and I don't think they need any further comment.

Growth of Prematurely Born Infants With and Without Retrolental Fibroplasia.

Dr. Lula O. Lubchenco, Dr. Edith Boyd, and Dr. Marion S. Dressler, Denver.

In searching for factors which might be related to the occurrence of retrolental fibroplasia, an analysis was made of the records of premature infants who had regular ophthalmoscopic examinations after admission to the premature nursery of Colorado General Hospital. The time of diagnosis after birth was plotted against gestational age at birth, and the central trend through

the scatter of cases indicated an inverse relation between gestational age and time of diagnosis. For example, infants born at 26 weeks of gestation were of 11 to 12 weeks postnatal age before the diagnosis was first made; whereas in those born at 33 weeks gestation the diagnosis was made five to seven weeks after birth. In 87% of 70 cases, diagnosis was made before the infant attained a gestational age of 40 weeks.

A study was then made of the rates of intrauterine and extrauterine growth of infants, in some of whom retrolental fibroplasia had developed. As a standard of reference, a curve of intrauterine growth was prepared using the birth weights and gestational ages of 3,690 infants born alive in the Colorado General Hospital during the five-year period from 1948 to 1952, inclusive. Information on 102 infants under 30 weeks gestational age at birth in other hospitals and admitted to the premature center was added after it had been demonstrated that their weights were similar to those of the Colorado General Hospital infants. When the 50th percentile of this standard was compared with Scammon's and Boyd's data, based on autopsy material, it was found to be slightly above the Scammon-Boyd curve, reaching a maximum difference of 300 gm. at 33 and 34 weeks gestation.

The birth weights of babies who received adequate eye examinations during a two-year period were then compared to the standard median. Almost all of the babies in whom retrolental fibroplasia later developed were below the median at birth, and the majority were of shorter gestational ages—very few being more than 34 weeks gestational age at birth. Although most of the babies who did not show signs of retrolental fibroplasia were also below the median, they were of longer gestational ages. In eight out of nine multiple pregnancies, the smaller baby showed the more severe disease.

Weekly rates of extrauterine weight gain were plotted for infants born at 26 and 27 weeks of gestation. All of these babies showed the usual initial weight loss and then tended to parallel the standard at a lower level but did not regain their original percentile standing during the period in the nursery.

The infants in whom retrolental fibroplasia developed were the smallest babies at birth, and there was minimal overlapping as they grew. Furthermore, they lost weight for a longer period of time, but as they approached a maturity of 40 weeks gestational age, they were gaining weight at a faster rate than the standard intrauterine median. Those in whom retrolental fibroplasia did not develop, by contrast, were larger at birth and were following the more gradual intrauterine curve when they reached 40 weeks gestational age.

DISCUSSION

Dr. Harry H. Gordon, Baltimore: I think, in these days when we are all so worried about postnatal environmental factors that may have something to do with this disease, it is interesting to have a report bearing on the question of host factors. The evidence this afternoon suggests that perhaps we are dealing with a disease that not only is a disease of small premature babies but of babies who are small for the degree of their prematurity.

It might also be worth pointing out that Dr. Reese has reported on two pairs of eyes, Dr. Owens and Dr. Friedenwald have one pair of eyes, and Dr. Ray Griffiths has one pair of eyes from a baby who lived for only nine hours, and in all four of these infants the early signs of retrolental fibroplasia have been found as described by Dr. Friedenwald and Dr. Owens, that is, a disorderly growth of capillaries. Thus, the early signs of the disease have been present at birth.

Dr. Edith Boyd, Denver: Dr. Lubchenco wanted me to add a few things about the problem of the character of the growth curve. Our biggest problem here, as you probably well realize, is the nature of the data, and why does that material differ from the old one established by Dr. Scammon? His material was chiefly from autopsies, and the body weight, as is well recognized, shrinks about 200 gm. from the time of the child's death until it is taken into the laboratory and weighed. I think that the curve we present here today is much closer to representing the real pattern of intrauterine growth.

I think we still have to go further than this particular study. I think we have to get our obstetrical friends to get histories a little more carefully for us and then let us set up a new standard so that we can really trust the history and see if we still get the same kind of curve.

If we do, we are breaking a long established concept, and that is that the child grows fast to birth and then slows up. We will now establish that he starts slowing up at 33 to 34 weeks of age. That makes quite a difference in our concept of normal growth from what we have had before. I think we have to put our paper forward as tentative, and then if we can get better material see if it verifies what we have found or changes our ideas again.

Parapertussis: Observation of Humoral Antibodies and Skin Reactions to Chemical Fractions of the Organism. ELEANOR WIXOM, M.S. (by invitation), ELIZABETH DAY, M.S. (by invitation), HENRY SCHERP, Ph.D. (by invitation), and DR. WILLIAM L. BRADFORD, Rochester, N. Y.

The results of a study of humoral agglutinin titers against Bacillus parapertussis and Hemophilus pertussis in a group of 531 subjects are described. This group is considered to be a representative sample from approximately 3,000 routine admissions to a general pediatric service.

Seven per cent of the subjects tested revealed titers of 1:320 or higher against B. parapertussis, as compared with 34% against H. pertussis.

In a group of 273 subjects immunized against pertussis but with negative history of the disease, 5% had titers in this range against B. parapertussis; but in an immunized group who also had a positive history of whooping cough, 13% had high titers against B. parapertussis. The difference suggests that certain of the latter group may have had parapertussis instead of whooping cough.

Of the group of 273 subjects immunized against whooping cough, it is estimated that 80% were actually protected against the disease.

The results obtained from skin testing with two different chemical fractions prepared for B. parapertussis suggests that this method may be of value in assessing immunity in parapertussis in a manner similar to that when agglutinogen is used to test immunity against whooping cough.

DISCUSSION

DR. HARRIET M. FELTON, Galveston, Texas: I am very glad to have a supporter for this agglutinogen question that we have had for so many years. All of us, I think, are working toward some method of early diagnosis in this very tragic disease that occurs in our children, and I think that here we may have something again which will not be of help in the first few days, but possibly might become a differential diagnostic agent for us.

We have been interested in following the skin reactions in these children with the pertussis agglutinogen, particularly in view of the fact that we often did not find a very high titer of antibodies in the sera of the children at the time that we skin-tested them, although many had a history of having had the vaccines or the disease. In retesting them a week after the skin test, we have had a marked rise in the titer. I wonder if Dr. Bradford has found the same thing with the new agent?

DR. AIMS C. MCGUINNESS, Philadelphia: Dr. Felton actually did the work on this problem in our clinic. Dr. Bradford, by careful skin test studies over a period of many years, has obtained a tremendous amount of information on both pertussis and parapertussis. This is an excellent example of willingness to gather data slowly and meticulously for long-range results, which certainly have been forthcoming in this report.

In the studies which were carried out in Philadelphia, when we were doing a great many agglutination titers for both pertussis and parapertussis, about 5% of our sera agglutinated B. parapertussis if they aggluinated H. pertussis. I believe approximately the same results were reported from Newcastle-on-Tyne in England. I think we all are in error in not really making an effort to pick up B. parapertussis by routinely culturing for this organism every time we culture for H. pertussis.

We have not had many cases of parapertussis diagnosed bacteriologically in Philadelphia. Again, I feel this is more because we haven't looked for the disease than because the disease isn't there.

I would like to know if Dr. Bradford feels the prevalence of parapertussis is sufficient to justify the inclusion of B. parapertussis in standard immunizing vaccines.

DR. IRVINE MCQUARRIE, Minneapolis: I recall very well when Dr. Bradford first became interested in the parapertussis problem. If I am not mistaken, he found that his own young son went to a party with a mild cough and a very high per cent of the children who had attended the party later came down with parapertussis. I wonder if there are certain years in some localities when we have more of it than others, like measles and poliomyelitis.

DR. JEROME L. KOHN, New York: At the Willard Parker Hospital we have been taking routine cultures for H. pertussis and B. parapertussis over a long period. In spite of the fact that H. parapertussis is much easier to grow and identify, it is rarely found in our labortory.

In our experience, the use of the pertussis agglutinogen skin test was a poor index of immunity during and after infection with whooping cough. The resultant test was positive in 63% of children. If more than two skin tests were done in one person, the resultant positive tests were much higher. As stated, the agglutinogen test was found to be positive following the use of pertussis vaccine in a large percentage of children. Apparently there is some antigenic substance in the vaccine that inflences the skin test.

Adult personnel on the whooping cough service with a history of whooping cough during childhood were found to have a negative skin test.

D.R WILLIAM L. BRADFORD, Rochester, N. Y.: I particularly appreciate the comments by Dr. Felton, for she had so much to do with the work on pertussis agglutinogen. Our observations of the antibodies in parapertussis somewhat agrees with her experience. We have not studied the response resulting from the skin test itself.

I appreciate the complimentary remarks by Dr. McGuinness. In reply, I may say that much of our work was stimulated by his work in Philadelphia and by that of Dr. Felton, now working in Texas. The proposal to include parapertussis antigen in pertussis vaccine has been made several times and has actually been carried out. To my knowledge none of the subjects reported in this study except the young infants we immunized had ever been given injections of parapertussis antigen. Unless parapertussis infection becomes more prevalent or more severe, I see no immediate necessity for the general practice of active immunization against the disease. At present the chief importance of parapertussis appears to be that it is often mistaken for mild pertussis.

In answer to Dr. McQuarrie's question I do not believe we have as yet determined the real incidence of parapertussis. Based upon our own data (positive cultures), it appears to be more frequent during the summer and fall months. At the present time both it and pertussis are rare in Rochester.

I agree with Dr. Kohn that the use of pertussis antigen as a test for susceptibility in pertussis leaves something to be desired. However, the experience with it has been, in the past, encouraging, and, in my opinion, it was unfortunate that it did not receive a more critical study, for we really have no other effective method.

Virucidal Activity of Some Common Surface Antiseptics, with Special Reference to Poliomyelitis. DR. HAROLD K. FABER and LUTHER DONG (by invitation), San Francisco.

Effective local antiseptics of skin and mucous membranes preparatory to injections and operations depends upon rapid bactericidal and virucidal action, since the usual interval between its application and the subsequent procedure is customarily brief, often not exceeding half a minute. There is reason to believe that at least some of the cases of poliomyelitis following tonsillectomy and injections of various sorts may have resulted from introduction, by the traumatic procedure itself, of virus already present on the surfaces; and, in the case of tonsillectomy, experimental evidence has been obtained that preparatory chemical disinfection of the surface might prevent this sequel.

The rapid virucidal effect of some commonly used antiseptics on poliomyelitis virus (Armstrong Lansing strain, Type 2) has been studied by mixing virus and antiseptic in varying proportions, diluting the mixture after one-half minute, and immediately injecting 0.03 ml. intracerebrally into white mice. The following materials were tested, with results as noted: 2% tincture of iodine, highly effective; tincture of thimersol (Merthiolate), moderately effective; tincture of mitromersol (Metaphen) and 2% alcoholic solution of hexachlorophene, slightly effective; tincture of benzalkomium (Zephiran) and 63 to 70% alcohol, ineffective.

For poliocidal purposes, 2% (mild) iodine tincture is recommended.

DISCUSSION

DR. AIMS C. MCGUINNESS, Philadelphia: I was very much interested in this study. At the meeting of the Armed Services Commission on Immunization held in Washington, D. C., several weeks ago, there was considerable discussion as to the best agent to use for cleansing the arm prior to vaccination against smallpox. Of course, when this procedure is carried out in the Army what cleansing there is to be done must be done fairly rapidly and easily. Dr. Kenneth Goodner brought out the point that benzalkonium 1 : 1000 had absolutely no effect whatever on vaccinia virus and that he considered it one of the best cleansing agents for the purpose available. He pointed out further that because of its wetting effect benzalkonium causes to spread out flat the little bubble of lymph which usually is so hard to break with the vaccinating needle. This results in much better contact of virus with skin surface.

DR. JOSEPH STOKES JR, Philadelphia: I was very much interested in what Dr. Faber had to say about iodine. In the studies carried out in Iowa, Texas, and Utah that were mentioned here on Tuesday, we used iodine, and I am interested in knowing whether Dr. Faber had any feeling as to whether the virus actually does get into the skin directly by needle in these cases of localization of paralysis presumably as a result of the injection of alum-precipitated toxoid.

I was glad to hear him say he felt injections of gelatin had probably no effect, and I think it may be worth while saying a word about the confusion on Tuesday (See the proceedings of the Society for Pediatric Research in this issue) in relation to the question of injection of gelatin in the controls during the gamma globulin field trials.

With the permission of Dr. McQuarrie, and after discussion with Dr. Faber, some clarification seems to be indicated.

Excluding the first week following the injections of gamma globulin and gelatin in the three areas studied, there were seven cases in the gamma-globulin group and 39 in the control group during the second to fifth weeks, inclusive. Dr. Weech mentioned that Dr. Sabin felt there was a great possibility, or he presumed there was a great possibility, that the gelatin injections may have made the difference between the 7 cases and the 39, in other words, increased the number of cases by 32.

While there are a number of reasons why this position does not seem tenable to us, the two following reasons are of primary importance. First, there has been no evidence to our knowledge that even such a material as alum-precipitated toxoid has actually increased the rates of paralytic poliomyelitis. There seems to be some evidence for such a material causing localization but it is not highly significant. However, there is no evidence even of localization in the limb where the injection was made as a result of such innocuous materials as gelatin. Gelatin is used as a plasma expander, and, as shown in the animal experiments discussed on Tuesday, there was no evidence of local inflammation in the areas where gelatin was injected.

In the group of 27,500 children given injections of gelatin no localization of paralysis in the limb where the injection was made could be demonstrated.

Second, we have an excellent comparison between the group given gamma globulin and the uninoculated group and in this comparison there is a highly significant difference between these groups if one separates out the Texas area on account of its low reporting of cases.

In Texas, judging the total number of cases in the uninoculated group from the number of deaths and amount of severe paralysis, it becomes obvious that there was a lack of reporting of the the paralytic cases of somewhere between 40 and 50%.

But if one adds all of the uninoculated groups together, one still gets a highly significant difference between the group given gamma globulin and the uninoculated group in favor of the former. So whether one uses as a control group those given gelatin or the uninoculated group, the evidence seems to us solid.

We feel that this is the first step in the direction of control of poliomyelitis. It gives a rationale for the future development of methods of control. If only a trace of antibody is effective in protecting against the disease, as demonstrated in our studies, then surely it may be possible to develop such traces for longer periods by means of vaccination or the combination of gamma globulin and vaccination.

DR. A. ASHLEY WEECH, Cincinnati: Having gotten into this fray on Tuesday by reporting some of the results of Dr. Sabin's last analysis, I think it is only fair that at this time I should go on to say that nothing that I said at that time should be construed to mean that I did not think the data were highly suggestive.

I cannot go over the data without saying that the word "highly probable" is justified, but I still don't believe that the words "the conclusions are solid" are justified.

I think there is considerable importance in this point of view, because if our conclusions regarding the gamma-globulin experiments are valid, there would be no reason for further studies or gathering of more data during the coming summer, and we could wind up without having any additional information.

It is true, as Dr. Stokes says, that Dr. Sabin's conclusions depend upon the hypothesis that the injection of gelatin in one group of children did enhance the number of cases of paralytic poliomyelitis that were observed.

Although this may seem highly improbable, if the hypothesis is made, then one finds it difficult to explain the entire results unless, indeed, one assumes in the uninoculated group that lack of reporting was the reason why that group differed so significantly from the other group, and that in itself is a difficult matter to assess.

Dr. Edward B. Shaw, San Francisco: When I left home, a child had just been dismissed from my service who had been admitted with poliomyelitis which followed vaccination against smallpox. Sure enough, the paralysis was localized to the vaccinated arm, the left, and involved mostly the deltoid and triceps.

It might be of some value to examine incubation periods following vaccination as compared to those which follow immunizing injections to see if there is any difference. In either case, if we are dealing with inoculation of the virus through the skin the incubation period should date from the moment of vaccination or immunization. On the other hand, if local injury due to the inoculation is the provoking cause, the incubation period should date from the time of the actual injection of diphtheria toxoid, etc., but should date only from the time the vaccination reaction reached its height. I suspect that this differential obtains.

I want to bring out the point that there is great variability in the effectiveness of various antiseptics with respect to different viruses. Tincture of iodine in dilute form seems to be very effective against poliomyelitis virus but completely fails to inhibit vaccinia virus.

Throughout all the early years of my practice I used tincture of iodine in the preparation of the skin before vaccination, removing the iodine at least partially with alcohol and then drying the area with ether. I was frequently assured that this would interfere with vaccination, but it never seemed to do so even though an appreciable layer of iodine remained on the skin through which the vaccinia virus was applied by multiple pressure, and acceptable takes resulted with dependable frequency. I finally stopped using iodine simply as a matter of convenience and substituted alcohol and ether or acetone, but since hearing of Dr. Faber's studies I have resumed the use of iodine for skin preparation.

There was an amusing experience a few years ago when a child in school was vaccinated inadvertently and was immediately found to be a Christian Scientist, who wasn't supposed to be vaccinated along with the other children. The vaccinator promptly applied tincture of iodine over the vaccination to kill the virus, but it proceeded to a successful take.

By contrast, as an indication of the selective effects of different antiseptics on viruses, if the alcohol which is used in skin cleansing contains the barest trace of formalin, the vaccination will almost invariably fail to take.

With regard to Dr. McGuinness' question, I think it might be good practice to use iodine for skin preparation before vaccination in accordance with Dr. Faber's data. Even though many may insist that this will interfere with successful vaccination, it won't do so at all.

Dr. Robert Ward, New York: Dr. Faber has been interested in portals of entry for many years, and now he is thinking of the possibility of the skin, in addition to the mouth and pharynx. I should like to ask him whether he thinks that the virus may be in the vaccines, in the needle, on the skin, or whether, possibly, it may be in the blood and localize beneath the skin in the area that is traumatized by the injection.

We have thought in the past that it was worth while looking for virus on the skin, and we have tested handwashings of children with the disease and of family contacts with negative results.

Dr. Herbert A. Wenner, Kansas City, Kan.: I enjoyed hearing Dr. Faber's paper. There are a couple of things that concern me and have for a long time. I have never quite been able to accept the injection of virus in the skin as a working hypothesis, despite the incubation periods that are shown.

I am not always sure that virus is injected from a site localized on the skin, and I am turning to Dr. Schick for a moment, because I have the impression that some time ago someone injected tetanus toxoid into animals and then subsequently sectioned the cord and showed there was a loss of chromatin and perhaps physiological disutrbances which may be quite similar to those seen following fatigue (in monkeys).

I have rather felt despite the current rage of viremia that the virus still enters the central nervous system along neuronal pathways. Perhaps in the patients who come down with segmental paralysis the virus is already localized in the central nervous system, remaining latent there and the stimulus (toxins or toxoids) injures the cell enough that the virus can set up housekeeping in the anterior horn cells as well as in others in the central nervous system.

Dr. Henry L. Barnett, New York. We have only recently been successful at The New York Hospital in getting iodine replaced by benzalkonium. Although Dr. Faber said that these were only preliminary results, I should like to ask him whether he would suggest that I, as a member of the formulary committee at The New York Hospital, recommend to the committee that we now replace benzalkonium with iodine.

Dr. Harold K. Faber, San Francisco: The number of cases of segmental paralysis following injections is too small to influence the over-all attack rate of poliomyelitis, and the ratio of the "double event," as the English call it, to all injections is also extremely small. Nevertheless, the relationship between injections and segmental paralysis is a real one, but it appears to result from some rather peculiar and unusual concatenation of circumstances. The inference that it may be due to introduction of virus at the time of injection is based partly on the usual interval between injection and onset, corresponding with the normal incubation period of poliomyelitis, and partly on the fact that the same picture can be reproduced experimentally.

A similar mechanism appears to be involved in post-tonsillectomy bulbar paralysis, as shown by experiments presented to this society two years ago. In these, tonsillectomy on monkeys immediately after application of virus to the throat was followed after seven days by typical bulbar paralysis, sometimes accompanied by high cervical, but without thoracic or lumbar, involvement. In another series, animals were infected by intracerebral inoculation and tonsillectomized three days later. In these a severe bulbospinal paralysis ensued after only two days, and involved all levels of the cord. The first group was believed to be comparable to the usual human post-tonsillectomy paralytic cases and suggested that in the latter the virus is introduced at the time of operation. The second group, with its very short interval, was thought to be similar to the rare and exceptional human cases in which paralysis supervenes within a day or two after operation, suggesting localization of infection already established. The latter mechanism might also occur after injections but, as indicated by the extreme rarity of very short intervals between injection and paralysis, is probably very exceptional.

In reply to Dr. Ward, it is my feeling that the source of the virus in cases of post-injectional paralysis may be the patient's own skin, as well as contaminated vial stoppers or needles. However, we have thus far failed to obtain positive tests for virus from the skin of patients and contacts in about 15 attempts, which does not, of course, exclude the possibility.

With reference to Dr. Shaw's comment regarding vaccinia, I have also found that preparation of the skin with 2% iodine does not interfere with takes. It may be noted that there are about half a dozen reports in the literature of segmental paralysis, usually of the deltoids, following vaccination.

In reply to Dr. Barnett, I feel that 2% (not 7%) iodine is the best of the local antiseptics because of its broad spectrum, being effective against both bacteria and at least the small viruses, whereas benzalkonium has value, so far as I know, only against bacteria. Certainly it is completely ineffective against poliomyelitis virus.

Factors Involved in the Production of Tissue Damage by Endotoxins Derived from Gram-Negative Micro-organisms. Dr. Robert A. Good (by invitation), Dr. Floyd W. Denny (by invitation), Dr. Richard T. Smith (by invitation), and Dr. Lewis Thomas (by invitation), Minneapolis.

In rabbits, a single intravenous injection of Gram-negative bacterial endotoxin causes fever and neutropenia. Occasionally with very large doses, animals react with prostration and death; no tissue lesions are demonstrable in such rabbits.

When two intravenous injections of endotoxin are given spaced 24 hours apart, the generalized Shwartzman phenomenon occurs. This reaction is characterized by bilateral cortex necrosis of the kidneys. The basis for the renal lesion appears to be occlusion of the glomerular capillaries by "fibrinoid."

Treatment of rabbits with cortisone caused a profound alteration in the reactivity to Gram-negative bacterial toxin. Instead of requiring two injections of meningococcal toxin for the production of renal cortex necrosis, in cortisone-treated animals this reaction developed after a single injection of toxin.

The possibility that cortisone exerted its effect through interference with an action of the reticuloendothelial system was considered. Using clearance of radioactive colloidal gold from the blood as an indicator, functional impairment of the reticuloendothelial system in cortisone-treated rabbits was demonstrated.

Treatment with agents capable of producing reticuloendothelial blockade had an effect similar to that of cortisone. A single intravenous injection of toxin following the injection of thorotrast, trypan blue, saccharated iron oxide, and India ink regularly produced the generalized Shwartzman reaction.

The possibility that "preparation" for the generalized Shwartzman reaction by intravenous toxin is due to interference with reticuloendothelial function was studied by two methods. In rabbits previously given toxin, the clearance of colloidal gold from the blood was found to be delayed. Moreover, the distribution of intravenously injected colloidal carbon was markedly altered in rabbits which had received toxin; instead of being taken up entirely by reticuloendothelial cells in the liver and spleen, large amounts of carbon were deposited in cells lining the glomerular capillaries.

Factors in the circulating blood may be of importance in the pathogensis of the generalized Shwartzman reaction. Implication of polymorphonuclear leucocytes was indicated by the observation that nitrogen mustard prevented the reaction completely. The observation that heparin, in anticoagulant doses, also prevents renal cortex necrosis suggests that an alteration of the coagulation mechanism may be involved in the reaction.

Following the demonstration that reticuloendothelial "blockade" prepared rabbits for the generalized Shwartzman reaction, it was found that in rabbits infected with Group A hemolytic streptococci the generalized Shwartzman phenomenon also developed after a single intravenous injection of meningococcal toxin. Under optimal conditions of dosage and timing, a necrotizing lesion confined to the coronary arteries occurred in a high percentage of rabbits. The lesion was characterized by deposition of masses of fibrinoid material beneath the intima, in the media, and in the periadventitial tissue. Similar material was observed in vegetations on the mitral and aortic valves. Segmental necrosis of walls of the coronary arteries accompanied the deposition of fibrinoid. The lesions were observed only in animals given streptococci followed by Gram-negative bacterial toxin; they did not occur with streptococci alone or when the generalized Shwartzman reaction was produced by two injections of toxin without streptococci.

DISCUSSION

Dr. Herbert C. Miller Jr., Kansas City, Kan.: I should like to ask Dr. Good if this eosinophilic staining material that he showed us in the glomerular tufts and other materials, and called "fibrinoid" by Dr. Angevine, could possibly be labeled hyalin, and, if so, did it appear in the lungs of these animals?

Dr. Charles A. Janeway, Boston: This paper opens many exciting possibilities.

I wasn't quite sure from what Dr. Good said whether it was possible to elicit the fibrinoid change by an injection of any streptococcal product following the initial infection.

The nitrogen-mustard experiments are of great interest because nitrogen mustard, although it is capable of inhibiting the formation of antibodies, has certain effects on disease which obviously cannot be explained on that basis. Dr. Chasis has shown that you immediately alter the kidney in chronic glomerulonephritis by use of nitrogen mustard. It doesn't seem likely to me that nitrogen mustard is knocking out the antibody mechanism so rapidly, and here you may be altering hematuria of renal disease by a much more immediate type of reaction.

Dr. Wallace W. McCrory, Philadelphia: I should like to second Dr. Janeway's comments and add that this information is not only stimulating, but also rather unsettling, particularly to those of us who are currently administering the various adrenal steroids in large doses to patients.

I should like to ask the authors in this regard whether they would consider the dose of 25 mg. to a rabbit to be, large or small? Would this effect be considered a physiologic or a pharmacologic action?

Dr. Robert A. Good, Minneapolis: I should like to thank the discussants for their kind remarks. In answer to Dr. Miller's question, one of the central points of our study has been the histochemical definition of the eosinophilic material. It is distinct from hyalin and possesses all of the characteristics of fibrinoid as defined by Angevine. Consequently, if such membranes occur in the lungs, they are not hyaline membranes in the strict sense. We have observed this homogeneous eosinophilic material in the lungs of some of the experimental animals in which the generalized Shwartzman reaction developed, but have not yet had time to do a detailed microscopic study of the pulmonary pathology.

In answer to Dr. Janeway, we have thus far been unable to produce these reactions with streptococci alone, nor have we been successful in doing this sort of thing with the refined streptococcal products. It may be possible with appropriate manipulations to produce such reactions using streptococci without Gram-negative endotoxins, but thus far we have been unable to do it.

As far as the effect of nitrogen mustard is concerned, we feel from the experiments described that the protective effect is mediated through the neutrophiles or something very very intimately related to them. We are unable to implicate the platelet system in the production of the generalized Shwartzman reaction, although we have carried out extensive studies in an effort to demonstrate a relationship.

Supporting the role of the neutrophile have been experiments with benzene, which, like mustard, also produces a profound neutropenia and will prevent the Shwartzman reaction. Interference with the neutropenic action of benzene, but not with its general toxicity, by the simultaneous administration of sulfapyridine, abolishes the capacity of benzene to prevent the Shwartzman reaction. If rabbits treated with either mustard or benzene are able to maintain a normal neutrophile count, the Shwartzman or generalized Shwartzman reaction can develop in them.

Dr. McCrory poses that sticker of a problem—are the actions of cortisone described of physiologic or pharmacologic significance? I don't really understand this difference. I can only say that the lowest dosage we have used to produce these effects in experimental animals has been in the neighborhood of 8 mg. per kilogram of body weight per day for three days.

We have obtained such results only irregularly with corticotropin (ACTH) and have not been able to mimic the cortisone effect in animals under repeated or prolonged stress, such as anoxia or chilling, prior to the injection of toxin.

The Biosynthesis of Hyaluronic Acid. Dr. Albert Dorfman, Saul Roseman (by invitation), and Sara Schiller (by invitation), Chicago.

The occurrence of the mucopolysaccharide, hyaluronic acid, in the capsule of streptococci, which appears to be chemically similar to the hyaluronic acid of mammalian connective tissue, has focused attention on the possible importance of this substance in rheumatic fever. Although such ideas have been advanced for several years, the paucity of knowledge regarding the metabolism of the mucopolysacharides has made it difficult to determine the details of the behavior of streptococcal hyaluronic acid. This report is concerned with a beginning of an attempt to elucidate the metabolism of the mucopolysaccharides. Our first efforts have been

directed toward a study of the mechanism of synthesis of hyaluronic acid by a strain of Group A Streptococcus (A111). The organism was grown on a semisynthetic medium to which was added precursors which were labelled in specific positions with radioactive carbon. The hyaluronic acid produced during growth was isolated from the medium and purified by a new procedure which yielded material of satisfactory purity as indicated by a variety of analyses including electrophoresis. Methods were devised for the isolation and degradation of various portions of the hyaluronic acid molecule. When 1-C_{14}-glucose was incorporated into the medium, it was possible to demonstrate that the glucosamine moiety arises from glucose without previous scission of the molecule. The isolation of the acetyl residue demonstrated that it arises largely from glucose with some dilution from other acetyl precursors. Since studies with 1-C_{14}-glucose did not yield definitive results regarding the origin of the glucuronic acid portion of the molecule, other experiments were performed utilizing 6-C_{14}-glucose. These led to the conclusion that the glucuronic fraction of the molecule also arises from glucose without previous splitting of the latter molecule. Subsequent experiments have been concerned with an attempt to determine the more immediate precursors of the polysaccharide.

Utilizing some of the information obtained in the above studies, experiments have been initiated to determine pathways of synthesis of mucopolysaccharides in mammalian tissues. Our first studies have been concerned with the mucopolysaccharides of the rabbit skin. Methods have been devised for the isolation of the mixed polysaccharides of this tissue. The administration of carboxyl-labelled acetate resulted in incorporation of sufficient radioactive carbon in the skin polysaccharides to permit study of turnover rates and mechanisms of synthesis.

DISCUSSION

Dr. Vincent Kelley, Salt Lake City: I should like to congratulate Dr. Dorfman. I think he has here a technique which is going to give us answers that many of us have been anxiously waiting for and seeking for several years.

I can see that Dr. Dorfman's work has not progressed to the point where he is going to have definitive answers for the questions I am going to ask. However, I am still going to ask him even though he will probably slough the questions like I did his the other day.

In acute disease, in rheumatic fever especially and in many other acute diseases, there occurs characteristically an elevation of serum hexosamines of which glucosamine is a major component. Very seldom is there an elevation of serum glucuronic acid during acute disease. I wonder if you have some ideas that you would like to express publicly as to what might happen here?

I have one thought with regard to this mechanism which I should like to express: glucuronic acid is known to be conjugated very commonly with 17-hydroxycorticosteroids. In view of the data that we presented here of elevated 17-hydroxycorticosteroids early in the course of rheumatic fever, for example, do you think it is possible that the 17-hydroxycorticosteroids are conjugating with the glucuronic acid and by the law of mass action forcing the reaction that would cause an elevation of hexosamines?

I should also like to ask whether or not Dr. Dorfman has an idea as to the relationships of serum mucoproteins to this system. We all know that serum mucoproteins contain a large fraction of hexosamine. Do you have any information or ideas as to the interrelationships here?

Dr. Albert Dorfman, Chicago: Thank you, Dr. Kelley, for your kind remarks.

As far as the first question is concerned, there has been, of course, a very wide speculation that the elevation of hexosamines result from the breakdown of connective-tissue polysaccharides. This, I think, superficially, is a very attractive idea. But at the present time one must look at this problem as follows: There is no evidence to support this idea—as a matter of fact, the evidence is quite to the contrary—that the mucoproteins are chemically quite different from hyaluronic acid.

I would point out in addition that I think such assumptions represent dangerous reasoning. That is, because something goes up in the blood and something happens in the tissue, the substance that goes up in the blood comes from the tissue. I don't think one would postulate, for instance, that the globulins which also rise come from hyaluronic acid.

I think I would say, in conclusion, that our primary reason for going to this great amount of detailed and difficult chemical work is that we feel that problems of just this kind cannot be attacked until such techniques are worked out. We think that with these isotope techniques we can probably supply in due time a direct answer as to whether the serum mucoproteins come from the connective tissue, but I am afraid this will have to be for some very distant meeting of the American Pediatric Society.

Nature of the Hemophilus Influenzae Cell Through Which Heritable Changes Are Induced by Deoxyribonucleic Acid. Dr. Hattie E. Alexander and Grace Leidy, A.B., New York.

There is now proof that deoxyribonucleic acid can change certain inherited traits in members of three different bacterial families, pneumococci, Hemophilus influenzae, and meningococci, and the indirect evidence suggests that genetic units of viruses are influenced by a comparable force.

The possibility is therefore raised that a comparable control of inheritance may apply to cells in general. The nature of the reaction which brings about a change in inheritance in bacteria therefore assumes great importance.

Our investigations on highly purified deoxyribonucleic acid H. influenzae in collaboration with Dr. Zamenhof suggest that the deoxyribonucleic acid itself plays the dynamic role of the gene or hereditary determinant, but the expression of the genetic change induced requires a substrate which is present in only a small proportion of the total population exposed.

Use of the deoxyribonucleic acid controlling streptomycin resistance as a genetic marker has offered a tool which lends itself to study of the quantitative aspects of the reaction which changes inherited characteristics. In a given population, the cells susceptible to the action of type-specific deoxyribonucleic acids and the streptomycin-resistance deoxyribonucleic acid show comparable frequency patterns. Therefore, the possibility is raised that the same cell is susceptible to each.

Evidence is presented for competition of Types A and B deoxyribonucleic and Types B and C deoxyribonucleic acids for the same cells. When populations containing susceptible cells are exposed first for 15 minutes to a type-specific deoxyribonucleic acid, the action of the deoxyribonucleic acid inducing streptomycin resistance is prevented. These results are interpreted as evidence that the same cell is susceptible to type-specific and streptomycin-resistance deoxyribonucleic acid and suggest that the susceptible cell is a specialized cell especially equipped for this purpose.

The specialized-cell hypothesis is supported by data which demonstrate failure of reproduction of susceptible cells under circumstances which permit rapid multiplication of the other members of the population. When the population size reaches $2 \times 4 \times 10^8$ the susceptible cells emerge, reach peak frequency within a short period, and slowly die unless they receive the stimulus of the deoxyribonucleic acid. The susceptible cell exhibits traits which are also characteristic of gametes or generative cells.

DISCUSSION

Dr. Charles A. Janeway, Boston: I don't think this paper ought to pass without a word of tribute, because this work is really pushing out the frontiers of biological knowledge in a very exciting way.

Dr. Hattie E. Alexander, New York: Last year Dr. Stokes asked me a question which I couldn't answer. In the last month, we have been able to answer it.

You remember last year we showed that rough Meningococcus cells could be changed into the type-specific epidemic form, Type I, with reproducible uniformity.

Dr. Stokes's question was whether these rough cells, which theoretically are not disease-producing, are changed into the type-specific form, Type I, which produces most of the cases of meningococcus meningitis during an epidemic. Can you demonstrate that the virulence has changed in some concrete way in the laboratory?

In the last month, we have demonstrated that the rough cells take on the virulence of Type I cells freshly isolated from spinal fluid of patients with meningitis, which are not virulent unless

used in very high dosage. When they are exposed for 10 minutes to a highly purified Type I deoxyribonucleic acid, the virulence is that which would be expected of freshly isolated Type I cells.

Studies on Klebsiella and Erwinia. Dr. Maragret H. D. Smith and Barbara Jo Holmes, B. S., New Orleans.

Several species of micro-organism have been shown to be pathogenic for both plants and warm-blooded animals. The morphological similarities between bacteria of the genus Klebsiella and the genus Erwinia, which comprises plant pathogens, led to a study of the interrelationships between the two groups.

Sixteen strains of Klebsiella isolated from hospital patients and eight strains of Erwinia originally recovered from infected plants were investigated. Homologous chicken antisera were prepared against 13 strains of Klebsiella and 8 strains of Erwinia. The results of quellung tests with these sera and the respective strains of both genera showed that many bacteria of the genus Erwinia exhibit quellung in the presence of many Erwinia antisera; but that they rarely "quell" in the presence of Klebsiella antisera. On the other hand, many strains of Klebsiella are "quelled" by antisera to Erwinia as well as to Klebsiella.

Several of the Klebsiella strains produced pulmonary lesions in mice when inoculations were done intranasally or intraperitoneally. Erwinia strains at the same dilution rarely did so. If, however, larger number of organisms were employed in the inoculum, many strains of Erwinia were also capable of inducing pneumonia in mice.

Studies were carried out on the pathogenicity of Erwinia and Klebsiella strains for sterile carrot slices, kept alive and moist in culture tubes. Four of the 16 Klebsiella cultures and 4 of the 8 Erwinia cultures inhibited normal proliferation and callus formation in the carrot tissues and caused discoloration and later death of the plant tissues.

Our data yield further evidence for the fact that the dividing line between bacteria pathogenic for warm-blooded animals and those pathogenic for plants may not be so sharp as was formerly thought. It seems likely that under exceptional circumstances bacteria which find their way into an unusual host may multiply and give rise to disease. Of far greater importance probably is the occurrence of antigens common to both plant and human pathogens; the frequent contacts during early life with plants and with insects and arthropods long recognized as the vectors of plant bacteria may promote the formation of antibodies against substances which are, under other circumstances, an integral part of human pathogens such as Shigella or pneumococcus.

DISCUSSION

Dr. Herbert C. Miller Jr., Kansas City, Kan.: I should like to comment on Dr. Smith's paper for two reasons. One is that I grow vegetables, and the other is that a few years ago Dr. Fawcett and I described a group of five or six infants under 4 months of age that had acute stomatitis from which we recovered an organism very much like the one that Dr. Smith reported from the throat cultures of the babies that she talked about.

This organism would kill mice very easily when injected intraperitoneally. We were not able to classify it in the usual Friedländer groups, and we have been very puzzled because we saw it in this series of five, or six, or seven babies all in a period of three or four months, and then we have never seen it since.

Dr. Walcher also reported on a group of babies with diarrhea from which he recovered an organism something like this. I wonder if Dr. Smith would be willing to comment on the possible pathogenicity of this organism for humans.

Dr. William L. Bradford, Rochester, N. Y.: One of my first investigative studies concerned otitis media in rats. The agent causing this infection was identified as a Friedländer-like organism which differed serologically from four of the main types then recognized. We used it experimentally to study the relationship of vitamin deficiency to infection.

I learned at that time that another Friedländer-like organism was responsible for metritis of mares.

I should like to ask Dr. Smith if Erwinia is related to such organisms found in species other than the human being.

DR. MARGARET H. D. SMITH, New Orleans: With respect to Dr. Miller's comment, we wrote Dr. Fawcett, I think, and were unable to obtain that particular organism, but from the description of it in the article by Dr. Fawcett and Dr. Miller, it must have been one of these very same Klebsiella strains.

We had occasion in Baltimore to observe a small epidemic due to one of these organisms on the wards of the Harriet Lane, while we were carrying out a cross infection study. We discovered the organism in far more patients than were made sick by it; we thought it responsible for mild clinical disease in several patients.

I suppose that small outbreaks of this sort must vary a good deal in seriousness, depending on the particular strain.

With respect to Dr. Bradford's comments, the Klebsiella-Erwinia group (which may in a few years be lumped together entirely, I think) certainly occurs widely in nature and causes not only disease in plants and in humans, but in moose, in deer, and in various rodents. These organisms are responsible also for all sorts of undesirable fermentations, and so forth, which take place in industrial and chemical industries, and in particular in the tanning industry.

Probably most of the time these bacteria are not terribly pathogenic, and it is probably the exception that they do cause disease in the particular host in which they happen to find themselves.

Prolonged Intermittent Corticotropin (ACTH) and Cortisone Therapy in the Nephrotic Syndrome: Immunologic Basis and Results. DR. KURT LANGE (by invitation), DR. LAWRENCE B. SLOBODY (by invitation), and DR. RUTH H. STRANG (by invitation), New York.

The nephrotic syndrome is characterized by marked proteinuria, lowered plasma proteins, and elevated serum cholesterol. These findings frequently persist after apparent diuresis.

Serum complement levels reflect the underlying antigen-antibody reaction. They are always lowered in the nephrotic syndrome, whether or not the underlying glomerulonephritis is apparent. The low complement levels are not due to loss of complement into the urine or lack of formation.

Twenty-four to 48 hours preceding spontaneous or drug-induced remissions, complement rises to or towards normal. Preceding relapses, complement falls again to subnormal levels. Serum complement levels thus become an excellent guide for therapy.

Corticotropin (ACTH) or cortisone-induced remissions are always preceded by a rise of complement to normal prior to the diuresis as an expression of the depression of antibody formation by the drugs (*32* courses in *25* patients, 100 mg. per day, seven days). If complement does not rise, diuresis does not occur.

In many instances, however, the corticotropin-induced remission is only of short duration, and antibody formation is rapidly resumed at pretreatment rate, as documented by the fall in complement levels.

Therefore, five days after the initial seven-day course of corticotropin, six patients with the nephrotic syndrome were treated with six to eight weekly courses of corticotropin (100 mg. per day for three successive days of each week). Of the six patients, in only one has the disease recurred after a severe otitis media. All others have not reaccumulated edema during the period of observation (9 to *29* months).

With this treatment, plasma proteins return only gradually to normal. The proteinuria and the blood cholesterol values decrease slowly. For the patient, hospitalization is prolonged.

To obviate some of these drawbacks, six patients were treated with 6 to 10 weekly courses of orally administered cortisone (400 mg. per day) on three successive days of each week subsequent to the original one-week course of corticotropin treatment.

All patients (five children, one adult) showed a rapid rise of serum complement to very high levels and an ascent of the plasma-protein value to normal within three weeks, a fall of the cholesterol value to normal within four weeks, and a rapid marked decrease of proteinuria. The appetite became ravenous, and there was a general feeling of well-being. One patient reaccumulated edema four weeks after cessation of therapy subsequent to a highly febrile upper respiratory infection. This child recovered spontaneously within two weeks of this episode with a return of serum complement to normal levels.

The patients are at present (three to five months after the end of therapy) free of clinical or laboratory signs of the nephrotic syndrome, except for slight proteinuria.

DISCUSSION

DR. CHARLES A. JANEWAY, Boston: I would like to congratulate Dr. Lange on a fine attempt to approach the treatment of this disease on a rational basis, based on the theory of its pathogenesis.

I would like to dispel one illusion that he left with you, that the measurement of serum complement is an easy test. There are considerable technical difficulties involved.

We can confirm (Dr. Wedgewood reported these results in a much smaller group of cases here last year to the Society for Pediatric Research) that serum complement rises under corticotropin treatment before diuresis begins, or almost coincidentally with it, and that this bears no relation to loss in the urine, because we have seen proteinuria increase or decrease, yet complement rises equally under either circumstance.

It is hazardous to draw too many conclusions from this. It suggests that we are dealing with a disease which has an antigen-antibody reaction as its pathogenetic basis. On the other hand, complement is such a complicated substance that you have to be careful about interpretation.

Dr. Lange is to be congratulated for trying to solve the therapeutic problem which remains after the use of cortisone and corticotropin, namely, that you have induced a remission but haven't cured the underlying disease process. By instituting this intermittent regimen and having a laboratory indicator to tell him when to institute treatment and what it does, he has apparently made some progress toward the goal of getting these patients over their disease without the continuation of overt symptoms.

One ought to stress several points. First, the doses of cortisone used are extremely large, particularly when given to children when they are nonedematous; 350 to 500 mg. is a great amount of cortisone per day.

The second point is that six cases are too few on which to draw any final conclusions that this is the optimal way to treat the disease. Everybody agrees now that in about 70 to 80% of the children diuresis can be induced with the administration of either corticotropin or cortisone in big doses for 10 to 12 days.

DR. JEROME L. KOHN, New York: I am a little disturbed by the high dosage of cortisone given by the authors, especially if continued after discharge from the hospital. Recently two children were discharged from the Mount Sinai Pediatric service with a maintenance dose of 75 mg. a day. On observation a week later, the systolic blood pressure in both children was between 175 and 185 mm. of Hg. When the cortisone therapy was discontinued, the blood pressure came down.

DR. WALTER HEYMANN, Cleveland: I agree with Dr. Janeway that the interpretation of the serum-complement depletion is difficult. Considering the excellent study of Ecker and Seifter on this subject, I would hesitate to discard the possibility that a good deal of complement is lost with the excretion of proteins in the urine of nephrotic children. Ecker and Seifter found that complement is not excreted en bloc, but that the four components are excreted in a different quantitative fashion. While C'2 is readily and C'3 and C'4 quite well excreted, C'1 is not found in the urine of nephrotic patients. For the detection of complement in the urine, the urine has thus to be supplemented with the C'1 fraction. Otherwise, the hemolytic activity would not show.

I would like to ask Dr. Lange whether he considered this point in his studies on urinary losses of complement.

DR. CONRAD M. RILEY, New York: I think that Dr. Lange's demonstration of the correlation between the edema and the complement level has been a fascinating thing. As we reported on Wednesday, we worked on the same problem ourselves and in general showed results very similar to Dr. Lange's using a different technique.

One question with regard to interpretation has bothered me. That is that four patients we saw very early in their disease, less than a month after showing any signs of edema, all showed normal complement levels at the beginning.

If this complement depression were actually entirely referrable to the depression of antibody-antigen combination, I should have thought that even early in the disease depression would already have been going on, and complement would have been depressed at that time. I think this is an interesting point, and I should like to hear Dr. Lange's opinion on it.

Dr. Robert Good, Minneapolis: I was very much interested in these results. I am sure we all were. However, I would like to add again a bit of caution in interpreting low levels of complement as an indication that an antigen-antibody phenomenon is going on. I think it is a very attractive hypothesis, but I am not certain that it is absolutely a demonstration of this relationship.

I would like to point out a very parallel situation with respect to the serum mucoprotein, which we feel has nothing to do with the antibody production. Very low levels of serum mucoprotein characterize the nephrotic syndrome. We have had opportunity to observe patients going into spontaneous diuresis, remissions of their disease, prior to the demonstrable decrease in a proteinuria—the mucoproteins rose in the serum, actually to elevated levels, and remained at normal or elevated levels during the entire period of remission.

We have had some similar experiences now under the circumstances of treatment with nitrogen mustard and with corticotropin and cortisone, and I think that there is a very striking parallelism between the behavior of acute-phase protein and complement in nephrosis. We know from Fischel's studies that complement behaves in other diseases as an acute-phase reactant, particularly in rheumatic fever, and I think these observations which Dr. Kelley and I published in the *Journal of Clinical Investigation* a few years ago would warrant consideration here.

Dr. Henry L. Barnett, New York: I think it is of interest that, whatever the mechanism, a number of people are getting the impression that prolonged or repeated treatment does produce better clinical results in these children.

As you know, Dr. Kramer has been doing this in a different way by giving a second full course after the initial course.

I think, again, that the evidence from physiologic data that the hormones may actually have some effect on the kidney lesion makes this reasonable to do, and, as Dr. Lange thinks, complement may be one indication for this.

Finally, although it has been stressed so much, I would say just one word about the complications of hormone treatment in these children. Special consideration must be given to infections, to which they are so susceptible, and to electrolyte disturbances which are different from the electrolyte disturbances that occur in children without nephrosis.

Dr. Wallace W. McCrory, Philadelphia: I should like to ask Dr. Lange one question. Experience with children who have received long-term therapy with either corticotropin or cortisone has led us to feel that such children are liable to show severer reactions with minor infections, and even fatal collapse states, than one encounters in children not so treated. Since it is now apparent that the adrenal steroids can be used to control edema in these children, the temptation to embark on long-term therapy is great. Consequently, we should be alert to the possibility that such therapy is as yet of unproved value and may be associated with serious complications, particularly as regards the capacity of these patients to resist bacterial invasion and withstand severe stress.

I should like to know in this regard whether Dr. Lange knows whether the episode of respiratory infection associated with a temperature of 105 F. observed in one subject was any more severe than similar episodes observed in this child before treatment.

Dr. Kurt Lange, New York: I am extremely grateful to the discussors for the suggestions made, especially to Dr. Janeway. The numerous discussions that I have had with him on this topic have been most stimulating.

The most important question resulting from the discussion seems to be the question whether the lowering of complement is actually an expression of some immunologic function, or whether the complement is lost into the urine, thus producing the lowered serum-complement level.

We have not found complement in the urine. Studies about the presence of individual components of complement in the urine are under way. We are well aware of the studies of Seifter and Ecker; if you take their figures and take the highest amounts of complement components

that they found in the 24-hour urine specimen in nephrotic persons, you will find, figuring backward, that the amount of individual complement components, especially C'2, corresponds to the complement contained in a few cubic centimeters of blood only. These figures can thus not be used as an explanation for the general lowering of complement. There are a few other factors which speak against such a hypothesis. Children who are almost anuric show very low complement levels even at the time of the severe oliguria. If complement were lost in the urine, you would expect that complement would rise at that time. This is not so.

The lowest complement levels are found in acute glomerulonephritis, with only traces of protein in the urine, and in the nephrotic stage with large amounts of protein in the urine you find much less depression of complement. These are but a few of the thoughts which we had concerning the lowering of complement and the possible loss in the urine.

We feel from the studies with the prolonged therapy that we should stake our aims of treatment of the disease higher than we used to do some time ago, namely, not just to relieve the edematous phase, but to try to cure the disease.

With 400 mg. of cortisone per day, we have had no untoward side effects except those mentioned. We have had slight rises in blood pressure, but none has forced us to stop the therapy. This may be just a lucky incidence in the cases we have treated so far, but we just have not seen any severe hypertension, since we have only treated for three days in succession.

As far as Dr. Riley's patients are concerned, namely the four patients in early cases who did not have a lowering of complement as yet in the very early phases, we have not seen this, but I would say I would expect that to happen. If the involvement of the glomerular surface is still very small, one would think that the amount of complement which the body produces normally and which covers all common antigen-antibody reactions without lowering of the serum-complement level, suffices in the beginning to cover also this reaction. Only when a very large antigenic surface comes into play, namely, the entire or a large part of the glomerular surface, so much complement is used in the reaction that the actual level falls.

As far as Dr. Barnett's and Dr. McCrory's questions about infections are concerned, I must state that all our children received 300,000 units of penicillin intramuscularly during therapy and 200,000 units of penicillin by mouth after therapy.

The infection which we described in one child with a 105 F. temperature took place three or four months after the termination of therapy, and it can certainly not be attributed to the cortisone therapy. However, we have the impression that these children while under cortisone therapy have a greater tendency to upper respiratory infections than a comparable normal group.

(To be concluded)

SOCIETY FOR PEDIATRIC RESEARCH

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Twenty-Third Annual Meeting, Atlantic City, N. J., May 4, 5, and 6, 1953

Second Session

Tuesday, May 5

(Continued from Page 357)

The Influence of Age on the Resistance of Rabbits to the Lethal Effect of Gram-Negative Bacterial Toxin. DR. RICHARD T. SMITH and DR. LEWIS THOMAS, Minneapolis.

In the course of investigations of the various effects of Gram-negative bacterial toxins in rabbits, it was observed that young animals tolerated intravenous injections of toxin in doses which caused extreme prostration and death in older animals. A study of the resistance of rabbits of differing ages to the lethal effects of meningococcal toxin was therefore undertaken.

In a representative experiment two groups of rabbits were employed: weanling animals 4 to 5 weeks old, averaging 0.5 kg. in weight, and older rabbits of the same stock 10 to 11 weeks old, averaging 2.5 kg.

Meningococcal toxin, prepared as employed for the production of the Shwartzman reaction, was injected intravenously in various dilutions in a 2 cc. volume. The results of the titration of toxin in the two groups of rabbits are indicated as follows:

Average Weight, Kg.	Age, Wk.	No. Rabbits Each Group	No. Dead After Dilution Indicated				
			1:20	1:40	1:80	1:160	1:320
2.62	9-11	8	5	5	3	4	3
0.5	4-5	8	0	1	0	0	0

There is evidence that protection against this class of toxins is a function of the reticuloendothelial system. Reticuloendothelial "blockade" by such agents as colloidal thorium dioxide (Thorotrast), colloid saccharate of iron, or colloidal carbon causes a striking enhancement of the lethal effect of Gram-negative toxins. It was postulated that if the greater resistance of young rabbits to the lethal effect of toxin reflects a greater protective capacity of the reticuloendothelial system than that present in older animals, then "blockade" of this system should eliminate the marked difference in susceptibility. In experiments designed to test this hypothesis, colloidal iron saccharate (Profferin) was used as a blocking agent. Groups of young and older rabbits comparable to those used in the previous experiment were given injections of colloidal iron, 2.0 cc. per kilogram of body weight. Six hours later these animals were given various doses of meningococcal toxin. The results of this experiment were as follows:

Average Weight, Kg.	Age, Wk.	No. Rabbits Each Group	No. Dead 24 Hr. After Dilution Indicated			
			1:320	1:640	1:1280	1:2560
2.60	9-11	4	3	2	2	0
0.59	4-5	4	3	3	4	1

Under these conditions there was no longer a significant difference in the susceptibility of young and older groups of rabbits.

This evidence suggests that the resistance of young rabbits to the lethal effect of meningococcal toxin may be due to an augmented protective function of the reticuloendothelial system in this age group.

The Role of Injections as Inflammatory and Localizing Agents. Dr. Morton Klein and Dr. Joseph Ziegler, Philadelphia.

Certain inoculation procedures have been implicated as factors that may localize the paralysis of poliomyelitis when given during the poliomyelitis season. Though the statistical data has implicated most often procedures involving immunization against diphtheria-tetanus-pertussis, some suspicion has been cast upon many other injected materials. The present work is an experimental study designed to evaluate various materials as inflammatory and localizing agents. Though the mechanism of the localizing effect in poliomyelitis is not clearly understood at the present time, our present awareness that a viremia may precede the onset of paralysis strongly suggests one hypothesis, namely, the inflammatory reaction resulting from the inoculation localizes the virus circulating in the blood stream. In the present work we have tested the following materials for their inflammatory and localizing activity when injected intramuscularly in 0.1 ml. amounts into the hind legs of white mice: (1) alum-precipitated diphtheria-tetanus-pertussis; (2) fluid diphtheria-tetanus-pertussis; (3) fluid diphtheria toxoid; (4) alum-precipitated diphtheria toxoid; (5) alum-precipitated tetanus toxoid; (6) fluid tetanus toxoid; (7) alum-precipitated pertussis; (8) fluid pertussis; (9) saline; (10) 1.5% gelatin; (11) aqueous penicillin G; (12) penicillin G procaine; (13) penicillin G procaine in oil and aluminum monostearate. At intervals varying from 1 to 31 days following the intramuscular inoculations the mice were given intraperitoneal injections of 0.2 ml. of a 1% solution of trypan blue. Four hours later the mice were killed and the legs removed and examined grossly for evidence of dye localization at the inoculated site; histological studies were carried out on a selected number of legs. A comparison of the severity of the inflammatory reaction following

alum-precipitated versus fluid vaccine indicated that in all cases alum markedly increased the severity of the inflammatory reaction and the degree of localization of the dye. The most severe inflammatory reactions were observed with (1) alum-precipitated diphtheria-tetanus-pertussis and (2) alum-precipitated pertussis. Both agents also effected an intense localization of the dye at the inoculated site. Though several of the other agents gave rise to inflammatory reactions (for example, alum-precipitated diphtheria toxoid, fluid diphtheria-tetanus-pertussis, and penicillin G procaine), in none of these cases was the inflammatory reaction severe enough to result in grossly visible localization of the dye. Saline, 1.5% gelatin, and aqueous penicillin G gave no significant inflammatory reaction and no localization of the dye.

Further studies are in progress to determine if the localization of the virus of poliomyelitis follows the pattern established by the trypan blue. We should point out, however, that the intense inflammatory and localizing agent, alum-precipitated diphtheria-tetanus-pertussis, has been implicated as one of the most important localizing agents in poliomyelitis. By contrast, 1.5% gelatin, a solution that did not give rise to either inflammation or localization, was not found to be a localizing agent of paralysis when used as a control inoculation in recent trials with gamma globulin. Finally, a recent Canadian survey indicates that fluid diphtheria-tetanus-pertussis is not a localizing agent, and in our study fluid diphtheria-tetanus-pertussis was found to be less of an inflammatory agent than the alum-precipitated antigen and to give little evidence of localization of trypan blue. It is therefore concluded that (1) the degree of inflammation determines the extent of localization of trypan blue and, by analogy, probably viruses; (2) the addition of alum to a vaccine increases the inflammatory and localizing action of the compound, and (3) if combined immunization is considered essential in selected cases during the poliomyelitis season, fluid diphtheria-tetanus-pertussis should be considered the lesser hazard as a potential localizing agent.

Bilirubin Encephalopathy (Kernicterus). DR. WILLIAM J. WATERS, DANIEL A. RICHERT, PH.D., and DR. HELEN H. RAWSON, Syracuse, N. Y.

Four cases of "kernicterus" resulting from hemolytic disease of the newborn were studied with particular attention to the character of the pigment staining the brain. Extracts of these latter areas were obtained in chloroform and Bloor's solution. A positive reaction to van den Bergh's test was obtained with such an extract. These extracts were then examined spectroscopically. Controls of crystalline bilirubin and normal brain in the appropriate solvents were run at the same time. In each of the four brains under study the curve found was consistent with that obtained from bilirubin. Crystals were prepared from one of the solutions. The crystals were then redissolved and reexamined spectroscopically and showed a curve identical with that of bilirubin as previously obtained.

It is suggested from our own clinical and experimental data, as well as those from the literature, that bilirubin itself, regardless of origin, under certain conditions is "toxic" in the immediate newborn period and more particularly in the premature and that the determining factors are as follows: (1) the degree of bilirubinemia which is a reflection of liver function and/or hemolysis, and (2) immaturity of the organism with a temporary defect in the hemato-encephalitic, or brain-cell, "barrier" associated with possibly inherent susceptibility of brain tissue.

The degree of and site of involvement determine the clinical course and possible sequalae, the implication being that there may be subclinical cases which escape diagnosis as a result. Since clinically and pathologically it is well known that areas of the brain other than the basal ganglia are involved, we suggest the term bilirubin encephalopathy as being more accurately descriptive from both viewpoints.

DISCUSSION

DR. RICHARD L. DAY, New York: The evidence presented that bilirubin was extracted from the kernicteric brains is certainly good. I should like to ask whether an attempt was made to extract bilirubin from the unstained portions of the same brains. Failure to find bilirubin in such areas would help to eliminate the possibility that the material extracted from the basal ganglia came from the vascular bed of the area and not from the actual pigmented brain cells.

As to the term "bilirubin encephalopathy," it implies that bilirubin is both the toxic and the staining agent. This may well prove to be true, but until the cause of kernicterus is established with certainty, it would seem best to me not to introduce another name for the condition. Multiple terms for the same thing often prove to be more confusing than the retention of an imperfectly descriptive designation.

DR. DAVID Y. HSIA, Boston: We are delighted to see this beautiful piece of work done by Dr. Waters and his co-workers. A year ago, we presented evidence to suggest that the kernicterus in erythroblastosis was probably related to the indirect components of the serum bilirubin. We have continued to have that experience and have not encountered any further cases of kernicterus in over 250 cases of erythroblastosis in which exchange transfusions were performed when bilirubin exceeded 20 mg. per 100 cc.

I think it is probably pertinent to add two other groups of cases which have been reported which demonstrated the relationship between bilirubinemia and kernicterus. One is the excellent group of cases reported by Crigler and Najjar, from Baltimore, in which they demonstrated kernicterus in all except one of their children, all of whom had very high levels of indirect bilirubin and in all of whom kernicterus had developed.

Also, Govan and Scott have reported on kernicterus without blood-group incompatibility in 10 premature infants. All showed hyperbilirubinemia and jaundice at the time of death.

In their controls, they studied a number of premature infants who suffered from anoxia and other evidence of distress, but with no jaundice or physical signs, and none of whom had actual staining in the brain. This all seems to add up to further evidence that indirect bilirubin is probably responsible for or is very closely related to kernicterus.

DR. HERBERT MILLER, Kansas City, Kan.: I should like to congratulate the authors on this and ask one question with regard to their willingness to speculate about whether the ready extractability of the bilirubin in the organic solvents they used has any implication as to the way the pigment may be bound in the cells.

DR. WILLIAM J. WATERS, Syracuse, N. Y.: With reference to Dr. Day's question, as I pointed out in the talk, we were well aware that we did not have adequate control in terms of brain tissue from a patient who had hyperbilirubinemia but did not have staining of the brain areas.

We have thought of taking unstained areas from the patient with pigmentation, but have wondered whether that would be a fair control, since our own feeling is that actually the brain tissue may have bilirubin in certain areas and that the bilirubin itself may not be grossly visible. We will certainly attempt to try areas that appear unstained grossly, but if we do get a reading for bilirubin, we are not sure that it would be a fair control.

We were hoping, of course, that the experimental "puppy" with hyperbilirubinemia would serve as a control, possibly, and are leaning a little bit heavily on the fact that since the brain did not appear pigmented grossly and since we were unable to obtain a bilirubin curve spectrophotometrically, that this, for the moment, might be the answer, although we wish to continue with Dr. Day's idea.

In answer to Dr. Hsia's comments, I should like to state that in three of the clinical cases presented, we did have the opportunity to have bilirubin levels done, and in the first case the bilirubin level reached the total of 33.4 mg. per 100 cc. before the patient died, and in the third and fourth, the levels were 22.4 mg. and 24.5 mg. per 100 cc., respectively, so that we, too, feel that the bilirubinemia has a considerable amount to do with the onset of pigmentation in the brain areas.

In reference to his remarks about indirect bilirubin, we were hoping that when we ran the van den Bergh reaction on the extract of pigmented brain we would not get any reaction in the one-minute specimen, but that it would be in the half-hour specimen, so to speak denoting indirect bilirubin, which certainly is the element that piles up in the blood. But, unfortunately for us, possibly, when we did do the microbilirubin test, we did get a reading in the 1-minute specimen, as well as in the 30-minute specimen, so that we took it to indicate that there was both direct and indirect bilirubin.

With reference to Dr. Miller's question as to whether we would like to speculate, we certainly would love to speculate, but I am afraid that we do not have sufficient evidence at the moment to make it worth while.

A Bacteriological Study of Acute Bronchiolitis in Infants. Dr. Sarah H. Wood and Dr. G. John Buddingh, New Orleans.

A careful bacteriological study was made of acute bronchiolitis in 51 children under 2 years of age. The children in the cases chosen for study had a history of a common cold for 2 to 12 days. Dyspnea, tachycardia, and emphysema were constant physical findings. Material from nasopharyngeal swabs and tracheal aspirations were streaked on freshly made Bordet-Gengou, Levinthal, and 5% rabbit-blood agar plates. The great frequency with which Hemophilus influenzae Types A and B were isolated from the specimens prompted an analysis of the serological response to these micro-organisms. The bacteriological and serological results obtained may be summarized as follows: H. influenzae, Type A plus an increase in specific agglutinins to Type A was found in 24 cases; no H. influenzae was isolated, but there was an increase in specific agglutinins to Type A in 11 cases; a rough amount of H. influenzae was isolated, but there was an increase in specific agglutinins to Type A in 2 cases; H. influenzae Type B plus an increase in specific agglutinins to Type B was found in 5 cases; no H. influenzae was isolated, but there was an increase in specific agglutinins to Type B in 2 cases; a rough amount of H. influenzae was isolated, but there was an increase in specific agglutinins to Type B in 2 cases; H. influenzae was isolated, but there was no increase in specific agglutinins in 3 cases; no H. influenzae was isolated and there was no increase in specific agglutinins in 2 cases.

Hemagglutination-inhibition titers against influenza virus A' (Cuppett) and B (Lee) were not significant in any of the paired sera, but against C (J. J.) there was a fourfold increase in titer in five patients.

Of the 36 pairs of sera tested for cold agglutinins, none showed a significant increase in titer.

The demonstration of specific serological responses to H. influenzae Types A and B seem to indicate that these organisms are involved in the infectious process. However, further investigation is awaited to clarify the problem as to whether or not influenza virus or other unrecognized viruses are implicated also in the pathogenesis of acute bronchiolitis of early childhood.

DISCUSSION

Dr. Andrew J. Rhodes, Toronto, Canada: This is an extremely interesting paper, particularly because it runs contrary to my own experience, and I wonder if some others feel the same way.

During the last winter we studied a series of approximately 30 cases of patients with laryngotracheobronchitis, all presenting with croup and with typical cases of the syndrome. Practically all required tracheotomy, and we obtained specimens from the trachea. We did not in these studies succeed in isolating any H. influenzae of any type, and virus studies also carried out were likewise negative. We ended up at the end of several months' work with practically negative results.

We have been unable to attribute the origin of these cases to any organism or virus. I should very much like to hear if my experience is typical or if perhaps we have just been carrying out insufficient work.

Dr. Francis F. Schwentker, Baltimore: Dr. Wood has presented very good evidence that the influenza bacillus was concerned in the cases of bronchiolitis she studied. However, one ought to be cautious about drawing too wide conclusions from this evidence. The bacterial flora of a community varies from year to year, and the predominant organism which causes the majority of infections one year may be rarely seen another year. We have seen cases of bronchiolitis which we are sure were due to other organisms. I should like to ask Dr. Wood if she believes that all cases of bronchiolitis are due to the influenza bacillus.

Dr. Hattie E. Alexander, New York: Dr. Wood's paper is of great interest to me also because it is contrary to our experience. I believe that this represents a very unusual experience. Were the isolations made within a relatively short period? In other words, does this represent a little epidemic of Type A H. influenzae?

We have been interested in looking for typable H. influenzae in young infants, particularly in those with bronchiolitis, because of Dr. Trask's experience a number of years ago, which you remember was before the different types were classifiable.

Even though Type A is a rare cause of any clinical variety of H. influenzae infection, it would seem to be the etiologic agent in this group of patients if the method of typing is a valid one. I wonder why the capsular swelling method was not used for identification of the type.

The rarity of R-strain isolations is also an unusual experience.

DR. MARGARET H. D. SMITH, New Orleans: I think that Dr. Wood's paper is very interesting, and I think that it raises in the minds of some of us a question which Dr. Alexander wonders about, namely, the role of different types of H. influenzae in respiratory infections.

From several years' experience in New Orleans and a brief visit to Puerto Rico, I wonder if the situation in those areas is the same with respect to H. influenzae as it is in the North.

I should like to speculate as to whether H. influenzae isn't perhaps a more frequent organism in the southern areas than it is in the North, or at least whether it doesn't play a more important role in respiratory disease in the South than it does in the North.

Whether there is a greater variety of types or not, I don't know; but disease due to H. influenzae seems to be relatively frequent in our area.

DR. SARAH H. WOOD, Louisiana: Thank you for these comments. We hoped our study would stir up some interest and serve as a stimulus to further studies in bronchiolitis, looking particularly for H. influenzae. We did not use cases of patients with croup. The criteria used for selecting the cases were enumerated in this paper.

In answer to Dr. Schweitker's question, I do not think that all cases of bronchiolitis are caused by H. influenzae. Dr. Buddingh and I feel that perhaps the problem is similar to that of pneumococcus and pneumonia. But, so far, the evidence is not sufficient to draw hard and fast conclusions.

In answer to Dr. Alexander's question, we had cases the whole year round. We started in November of one year and accepted cases through December of the second year. New Orleans is a particularly good place to study this disease, because we seem to have it all year round. Some of our cases occurred in June, some in August, and some in October. However, the greatest incidence was found during the winter months of November, December, January, and February.

It is possible, of course, as Dr. Smith pointed out, that we have more infections with H. influenzae than do other parts of the country. Dr. Buddingh and I felt that a more deliberate search for H. influenzae would be rewarding. For this reason, the swabs were transferred to Levinthol's broth immediately after collection. This procedure perhaps increased the number of positive isolations.

Dr. Smith, of course, added a touch of local color which may help explain why we found so many cases of H. influenzae infection not found in other parts of the country.

Experimental Production of Porphyria in the Rat. DR. ROBERT A. ALDRICH, DR. JAMES A. CASE and DR. RICHARD A. NEVE, Portland, Ore.

In mature Sprague-Dawley rats receiving daily oral doses of Sedormid (allylisopropylacetylcarbamide) clinical and chemical changes develop which closely resemble human porphyria. The urinary excretion of coproporphyrin rises to a high level within a few days. At least 85% of the coproporphyrin is of the Type III isomeric configuration. Uroporphyrin, normally present in urine in only slight traces, is excreted in huge quantities after a variable lag phase. There appears to be considerable difference in the susceptibility of the animals to the same dose of the drug. As a result, the lag phase is not always predictable. Massive excretion of uroporphyrin develops abruptly soon after the appearance of a strongly positive porphobilinogen test in the urine. Most of this uroporphyrin is excreted as a colorless chromogen which can be converted to uroporphyrin by heating at pH 5.0. The methyl ester of this uroporphyrin has been crystallized, chromatographed, and identified by its spectrum and other physical properties as the Waldenström "uro-type" porphyrin.

Clinically, weakness of the hind quarters develops in the animals coincident with the appearance of porphobilinogen in the urine. At the same time, the fur on the abdomen begins to be stained a reddish-brown from its contact with urine. If the drug is continued, death follows, and at autopsy gross dilation of the gastrointestinal tract is a prominent feature. On

the other hand, if the drug is withdrawn at the peak of the illness, porphyrin excretion quickly becomes normal, porphobilinogen disappears from the urine, and the animal makes a complete chemical and clinical recovery.

We wish to present preliminary data bearing on the quantitative and qualitative aspects of porphyrin metabolism in these experimental animals. The use of this new experimental animal in the study of the metabolism of certain iron-porphyrin compounds will be discussed.

DISCUSSION

DR. WALTER HEYMANN, Cleveland: I should like to ask Dr. Aldrich two questions: first, whether or not porphyria develops in every rat that does receive Sedormid, or whether there is, in other words, individual resistance; second, whether or not he has any observations on age-conditioned differences in developing porphyria in rats by means of Sedormid.

DR. SCHMID, Minneapolis: I have been much interested in Dr. Aldrich's beautiful presentation. As he has mentioned, we have reported very similar results in rabbits. In fact, it seems that in rabbits, rats, and mice the same abnormalities of porphyrin metabolism in response to Sedormid develop. This is in contradistinction to guinea pigs, which, owing to their high sensitivity to sedatives, succumb to the sedative effect of the drug before abnormalities in porphyrin metabolism become manifest.

One of the aspects of this problem in which we have been particularly interested in the last half year is the mechanism of the porphyrin formation in the liver, particularly in relation to the human hepatic porphyria. From our studies in the animal it is obvious that the hepatic porphyrin formation probably has nothing to do with hemoglobin metabolism. There is no anemia; the porphyrin content of the bone marrow and the circulating erythrocytes is normal, and the bone-marrow morphology is not altered.

We have begun to study the metabolism of other heme protein compounds such as catalase and cytochrome C. To our surprise, the only striking and consistent abnormality in Sedormid-poisoned animals is a very sharp decrease in hepatic catalase activity. Within three to five days of continued drug administration, the catalase activity in the liver drops to values of 5 to 10% of normal. This drop usually precedes the massive uroporphyrin excretion in the urine. The catalase concentration of other organs, for example, the circulating erythrocytes and the kidneys, is little or not at all changed. The cytochrome C content of the liver remains stable, even after continued Sedormid administration for as long as four weeks.

As soon as the administration of Sedormid is withdrawn, if the animal has not died of the disease, the catalase concentration of the liver again reaches normal values within a few days, and the excessive porphyrin excretion ceases.

It seems from these preliminary studies that Sedormid may interfere with catalase formation in the liver in a fashion perhaps similar to the interference of lead with hemoglobin synthesis in the marrow. As a result of this blocking effect, porphyrin accumulates in the liver and is then excreted in the bile and in the urine.

There is one point I should like to make, and this is one of caution. As Dr. Aldrich has pointed out, one of the main objectives in producing an experimental hepatic porphyria is to provide a laboratory animal the study of which can give us some hints as to the pathogenesis and possible treatment of hepatic porphyria in humans. There are, however, certain differences between the experimental and the human porphyria which, at least at the present time, do not permit us to extend indiscriminately conclusions drawn from the animal experiments to the human disease. In the three or four cases of human acute hepatic porphyria which we have had a chance to study lately, the liver catalase activity was decreased to some degree, but since the biopsy material was obtained only some time after the acute attack had already subsided, the significance of this finding is difficult to evaluate.

Congenital Toxoplasmosis: A Study of One Hundred Three Cases. DR. HARRY A. FELDMAN, Syracuse, N. Y.

This report is based upon the analysis of 103 cases of congenital toxoplasmosis selected on the basis of positive serological (dye test) findings. The specimens were received from various parts of the world, and since complete information was not supplied in all instances,

it will be noted that the calculations which follow generally total less than 103. Among 101 patients 77 (76%) were in the age group 0 to 4 years, 16 (16%), 5 to 9 years, and 8 (8%), 10 to 17 years. Of these, 35 patients were studied during the first year of life. The sexes were represented equally with 51 boys and 50 girls. Prematurity occurred in 31%, and of these 27% died, whereas 12% of those born at term died. Seventy-four per cent of the mothers were between 18 and 29 years of age and 26% between 30 and 39 when the affected child was born. Chorioretinitis was noted in 99% of the patients, cerebral calcification in 63%, psychomotor retardation in 56%, hydrocephaly or microcephaly in about one-third each, and convulsive disorders in one-half. The chorioretinitis was bilateral in 85% and equally distributed between both eyes when unilateral. Among 191 patients with chorioretinitis, 45% had congenital toxoplasmosis. Among 115 patients with cerebral calcification, 50% had congenital toxoplasmosis. No congenital anomalies were noted among 46 patients with congenital toxoplasmosis. None of 35 children born subsequently to the mothers of patients with congenital toxoplasmosis were abnormal.

Among the mothers, 85% reported no illness during the pregnancy which produced the offspring with congenital toxoplasmosis. The remaining mothers had had either respiratory illnesses or, in one instance, Hodgkin's disease, and in another, chorioretinitis. Exposure to animals during their pregnancy was reported by 71% of mothers and denied by 29%. Infants with congenital toxoplasmosis were born in all months of the year so that the possibility of contracting congenital toxoplasmosis does not appear to be limited to any one season.

DISCUSSION

Dr. Heinz Eichenwald, Cornell, N. Y.: I should like to thank Dr. Feldman for his interesting study. However, I should like to add a few comments based on our observations on 130 cases of toxoplasmosis that have been identified in our laboratory in the last four or five years.

Like Dr. Feldman, we have been dependent, to a great extent, on material submitted to us by a large number of different physicians, and it can readily be understood why statistics obtained with such a "mail-order" service are influenced greatly by the opinions of these physicians as to what congenital toxoplasmosis should look like.

For example, it is very widely believed that toxoplasmosis, even in the newborn period, is manifested only by symptoms and signs referable to the central nervous system. This, of course, is not true.

We have been very interested in acute toxoplasmosis in the newborn, chiefly with a view to therapy, and have been able to transmit this interest to a number of physicians in our area. We have, therefore, been receiving many sera from infants with symptoms suggestive of acute toxoplasmosis such as fever, lymphadenopathy, hepatosplenomegaly, pathologic jaundice, anemia, rashes, convulsions, etc. These symptoms usually occur at birth or are noted within the first few days of life.

It is in this group of infants that chorioretinitis occurs in only about one-half the patients. We have followed many of them for periods as long as three to five years, and chorioretinitis develops in later life in few of this group.

We agree that with time many of these infants can be shown to have central nervous system damage. This is usually manifested by psychomotor retardation, and about 80% of these children can be found to be defective. About half will have convulsive episodes at some time in the first three years of life.

Dr. Forrest H. Adams, Los Angeles: At this time, I should like to congratulate Dr. Feldman for his good work on the subject of toxoplasmosis. As most of you know it has been very extensive.

This work just reported, however, implies that the triad of symptoms: cerebral calcification, convulsions, and chorioretinitis, should be present in order to make a diagnosis of toxoplasmosis. On the basis of studies made by our group at the University of Minnesota, I think these criteria are too strict and limiting. We found that the triad was commonly not present, but rather that hydrocephalus was most often present.

Since this work just reported concerns mainly tests on blood samples for their antibody content, I wonder if Dr. Feldman cares to make any comments regarding the specificity of the test? In our studies we were impressed with the high incidence of positive reactors using the dye test in pregnant women and in children with rheumatoid arthritis.

Another question concerns the incidence of positive reactors in various localities, this independent of clinical disease. Likewise, what is the relationship between the antibody titer and likelihood of clinical disease?

DR. HARRY A. FELDMAN, Syracuse, N. Y.: One point which I tried to make, and perhaps I should reiterate it now, is that the diagnoses were made on the basis of serological findings. There will be variations between different series of cases, depending upon how they are selected. But the fact remains that there are many cases of congenital disease that do not have the so-called "classic signs" of congenital toxoplasmosis.

With regard to Dr. Adams' opening statement, it is I who shall have to bear the responsibility for what was said this morning, and not Dr. Sabin. I don't know whether he would agree with everything that I presented. We know of no instance in which we have encountered nonspecific reactions with the dye tests. In instances in which it has been possible to detect a patient with acquired toxoplasmosis and in which early serum samples were available, the results of the tests have usually been negative.

With regard to the high incidence of toxoplasma antibodies among pregnant women and children with rheumatoid arthritis, we have been unable to demonstrate that they are different from "normal" populations.

Another kind of study which we are doing is of the toxoplasma antibody pattern of a normal urban population with equal representation of all age groups. In other instances where normal populations have been studied, the sample has been restricted to one age group or another.

There is an accumulation of positive reactors with increasing age in this particular population; in general, children, being closer to the time of acquisition of infection, have the higher titers.

The mothers of young children with antibodies were studied as well and were found either not to have antibodies or to have them in such low titer as not to be indicative of a congenital infection in the appropriate child.

We have completed a number of similar population studies representing eight different population groups, including Alaskan Eskimos, and the people of Iceland (low dog population), four different cities of America, Haiti, and Tahiti. Seventy per cent of the over-all Tahitian sample shows antibodies, but by the time the children of Tahiti reach 4 years of age, 90% of them have antibodies in high titer. This would lead one to suspect that congenital disease would be rather rare on that particular island.

We have since undertaken an additional study in another American area, among Navajo Indians, who live under rather impoverished conditions. There, much to our surprise, we have been able to find only two positive reactions out of 115 persons tested so far, including the crucial age groups of 20 to 40.

I should like to reiterate that we still must know more about normal populations, but the fact remains that at present it appears that congenital infection is only a very rare manifestation of what is really a very commonplace disease.

The Contributions of Filtration Rate and Tubular Activity to the Control of Electrolyte Excretion. DR. SAMUEL J. FOMON, DR. CLARK D. WEST, and DR. S. A. KAPLAN, Cincinnati.

The basic mechanisms of renal electrolyte control have remained obscure largely because of the lack of a satisfactory means of measuring tubular activity with respect to electrolyte. In the absence of a measure of tubular activity, it has been impossible to determine the relative contributions of filtration and tubular activity to the control of electrolyte excretion. The study reported represents a new approach to this problem, not based on the assumption that tubular activity remains constant with time, but, instead, that at a given point in time tubular activity will be the same in each kidney of the experimental animal. Such an assumption of bilateral equality of tubular function seems reasonable when one considers that those factors known to modify tubular control, whether hormonal or physicochemical, are systemically distributed

and in all likelihood exert their effects equally on each kidney. On the other hand, filtration rate, the other variable presumed to modify electrolyte excretion, frequently differs in the two kidneys, presumably a result of inequalities in vasomotor tone.

In the present study, significant differences in filtration rate on the two sides were encountered in 35 or 52 paired collection periods during experiments performed on nine dogs. Analysis of the paired data disclosed that the kidney with the greater filtration rate excreted the greater quantities of sodium and chloride, but that the difference in excretion was in general small and seemed to be variable.

To gain an understanding of the nature of the tubular regulation, the data were analyzed for a variable of physiologic significance, equal on the two sides, which would serve as a basic expression of tubular activity. Earlier studies by others suggested the direction of the analysis. Wesson and Anslow, and later Rapoport, observing the electrolyte composition of the urine during diuresis produced by mannitol loading, expressed the opinion that the renal mechanisms concerned with electrolyte control might be related to the concentration difference for electrolyte between tubular fluid and plasma. Calculations were therefore made of the electrolyte concentrations and volumes of the fluid issuing from the functional proximal tubules of each kidney. The calculations were based on the now generally accepted view that at the end of the proximal tubule, a region we have designated as the t_o point, the tubular fluid is isosmotic with plasma and that during the passage of the fluid through the distal tubule only water is reabsorbed. It was shown that the tubular fluids were in general equal in their concentrations of sodium (or chloride).

In summary, the bilateral equality of the concentrations of sodium (or chloride) in the tubular fluids of kidneys subjected to identical environments and stimuli, independent of differences in their filtration rates, suggests that the concentration difference for an electrolyte between tubular fluid and plasma is a variable of physiologic significance and may be considered a basic expression of tubular activity.

DISCUSSION

Dr. Henry L. Barnett, New York: I think that this approach to the problem is certainly of interest. With use of usual clearance techniques, it has not been possible to distinguish between the role of changes in glomerular filtration rate and in the rate of tubular reabsorption of electrolytes in controlling the rate of electrolyte excretion. This is due to the fact that glomerular filtration rate cannot be measured accurately enough to make a differentiation.

I should like to ask, in the first observation, where the right kidney had a considerably higher rate of glomerular filtration and where the tubules of the right and left kidneys were being exposed to the same hormonal and other factors, what told the tubule on the right side to reabsorb more water and sodium than the tubule on the left side?

Dr. Wallace W. McCrory, Philadelphia: I should like to ask the author if he feels that this method of examining the relationship between differing filtered loads and rates of tubular excretion provides data that can be interpreted to show the effect of changing glomerular filtration rate during an experimental procedure. The authors have examined the calculated rates of tubular excretion observed where spontaneous differences in glomerular filtration rate in the two kidneys of an experimental animal were found. The assumption of constancy of tubular activity in both kidneys under such circumstances is reasonable, yet it is qualitative, not quantitative. While this approach is unique, I should question whether one can interpret the data in terms of evaluating the importance of a change in glomerular filtration rate on rate of tubular excretion. In these observations, glomerular filtration rate was not altered. Instead, differences in glomerular filtration rate have been observed under experimental conditions.

Dr. Samuel J. Fomon, Cincinnati: Dr. Barnett asked perhaps the most significant question that could be asked.

The question was, how does the kidney on the left know that it should reabsorb more water and electrolytes than the one on the right? According to the argument just presented, the tubular control of electrolyte excretion depends solely upon the establishment of a concentration

difference for electrolyte between tubular fluid and plasma. It is inherent in this view that if one kidney filters greater quantities of electrolyte, greater quantities will be reabsorbed by that kidney in the tubular process of establishing a bilaterally equal concentration difference.

Circulating Adrenal Hormone in Children in Health and Disease. Dr. R. Klein, Dr. J. Fortunato and Dr. C. Papadatos, Pittsburgh.

The method of Nelson and Samuels was used to measure 17-hydroxycorticosterone-like (Compound-F-like) substances in the blood of 41 normal children and adults, 23 cord bloods from children born of normal deliveries, 13 specimens from 16 newborn infants, 16 from children with meningitis, 6 from children with acute severe respiratory infections, and 13 from children 24 hours after operations. In addition, measurements were made on the blood of five adults 24 hours after operation.

The average and the range of serum 17,21-dihydroxy-20-ketosteroid, for the normal children and adults were not significantly different from previous reports. The mean was 13 ± 1.21γ per 100 cc., with a range of 0 to 29. There was no apparent difference in any age group from one month to adult life. The levels obtained from cord bloods also did not significantly differ from the levels in normal controls. However, newborn infants from 12 hours to 5 days of life showed extremely low levels of circulating 17-hydroxycorticosterone-like substance. Most of them had no measurable levels. The one 7-day-old baby from whom blood was obtained had a level in the middle of the normal adult range.

Meningitis uniformly produced a striking rise in circulating 17-hydroxycorticosterone-like substances. The range was 45 to 168 γ per 100 cc. None of the patients with meningitis died. Three had meningococcemia. The six patients with acute respiratory infections also showed marked elevation in their circulating hormone, although patients with minor respiratory illnesses or patients examined with subsiding infections gave levels that were usually in the upper part of the normal range.

A variety of operations produced a rise of circulating 17-hydroxycorticosterone when measured before and 24 hours after operation. The average level 24 hours after operation was significantly elevated, but there was some overlap of the lowest postoperative values and the higher normal values. Only one adult out of five exceeded the normal range 24 hours after major abdominal surgery.

Children apparently respond to stress with an elevation of circulating adrenal hormone more readily than adults. This may imply greater ability of the adrenal to respond or slower conversion or utilization of equal amounts of hormone.

Newborn infants have low circulating 17-hydroxycorticosterone-like substances, as has been suggested by indirect measurements in the past.

DISCUSSION

Dr. Robert S. Ely, Salt Lake City: I should just like to say, in agreement with Dr. Klein, that we have had our mean values agree with him; the standard area in our range of distributions is pretty well in agreement.

As far as his question as to whether these values in the acute illness in adults were obtained early enough, I think I should say yes. The Nelson-Samuels clinical cases were obtained earlier, but they did not obtain very high samples.

We have had some high values, many more high values in children than have been obtained in the adults. However, we have had really too few acute illnesses for me to say anything to Dr. Klein on that score.

I notice that the values in the very newborn age groups were very low, and I should like to ask Dr. Klein what the mean value of those 10 newborn babies was. I should also like to ask if he obtained any particular correlation, or what their experience has been in correlation with eosinopenia involving corticotropin (ACTH) and epinephrine.

Dr. Albert Dorfman, Chicago: I should like to ask whether there are any data available in these studies on the reproducability of determination on a given person. That is, what values do you obtain if you take a given normal person on successive days? Also what are the effects

of time of day, time of eating, and, particularly, body temperature, which may have a great variation in affecting the results in disease? What are the effects of drugs in the patients being treated for infection?

I realize this is a big order and very difficult with a method of this kind, but I think it is rather important before any conclusions are drawn between the relation of infection or changes in adults and children to control some of the factors, since in many of the things that have been studied, such as eosinophile counts, these apparently superficial factors are sometimes important.

Dr. Robert Good, Minneapolis: I am very much interested in the very low values obtained in the newborn, and I should like to ask the authors whether or not they have had an opportunity to do studies on newborn babies with acute disease, such as septicemia, and whether or not these patients are able to respond.

I realize that time probably has not permitted the accumulation of such data, but I think it would be extremely important in the light of the present findings.

Dr. Nathan B. Talbot, Boston: I should like to ask the authors whether they think that the tendency toward functional quiescence of the adrenal cortices during the neonatal period is indicative of functional inactivity during intrauterine life.

Dr. Alfred M. Bongiovanni, Baltimore: I have a number of misgivings in regard to drawing too many conclusions on the basis of this method of determining blood levels of corticoids. Among them is our own experience with Cushing's syndrome, a disease in which we have been unable to find a regularly elevated level of blood corticoids. It appears that even should the urinary excretion of corticoids be high, the blood level is not necessarily elevated, which brings up one important question: What influence does the excretion of these substances have on the blood level? May the production of these steroids by the adrenal be high without it being reflected in the blood level? It is also to be remembered that the method employed measures only the free unconjugated compounds. Should a normal secretion of corticoids be accompanied by inadequate conjugation, one may conceivably find an abnormally high blood level with this method. In chronic liver disease it appears that conjugation may, in fact, be compromised, as was shown in the decreased urinary glucuronides in studies we conducted at the Rockefeller Institute a few years ago. Conversely, were one to find a diminished level of blood corticoids, does this imply poor adrenal function? Might not the total corticoid level including the conjugates be normal or high? Although the method employed may be helpful, more study is needed in basic methodology before it may be applied as a true measure of adrenocortical function with confidence.

Dr. Vincent Kelley, Salt Lake City: It is true that in the orginal report of Samuels and Nelson and their group it was stated that terminal patients were the only persons who had elevated levels of 17-hydroxycorticosteroids. In more recent studies, however, they have observed occasional elevations in sick adults, and, considering their entire group of sick adults, they have shown elevations which are probably significant. Dr. Tyler reported yesterday his results in postoperative cases. These were very similar to the results reported here by Dr. Klein.

In our group of children with whom we have been working, as Dr. Ely said, we find elevations in those acutely ill. In this regard the interesting observation has been made in patients with rheumatic fever that during the very early days of their rheumatic fever they have elevations of these steroid levels, whereas a few days later they have them no longer.

We have not studied a large group of young infants with regard to their blood steroid concentrations. However, we have done corticotropin response tests in small infants and find that they are capable of responding as adequately as or, probably, more so than adults. This is not a statistically validated statement, but, rather, it is an impression.

The variation in blood levels that one observes in normal presons is such that it is very hard to say that an individual sample from a sick patient is abnormal. Only when several sick patients who can be classed as a uniform group are studied and the date treated statistically can one be certain that elevated levels are not due to change alone.

The mean 17-hydroxycorticosteroid concentration in normal children reported by Dr. Klein agrees exactly with that observed by us in children. It also agrees exactly with the figures that Samuels and his group have observed in adults. They have studied 279 adults and found a mean value of 13.0, which is exactly the figure that Dr. Klein reports. Their 95% range in this group of adults is from 3 to 25γ per 100 cc. This means that a value of over 25γ per

100 cc. is suspect but not considered definitely abnormal. The same situation obtains with our group of children. When we observe a value higher than 25γ per 100 cc., we become suspicious. However, even if a single value is as high as 40γ per 100 cc., we cannot say it is definitely abnormal, because we have seen values this high in patients who clinically are normal.

We have a great deal of data with regard to diurnal variations of steroid levels. Persons followed throughout the course of the day have lower values through the late part of the day than they do in the morning. We have a large number, approximately 50 persons, who have been followed from 8 a. m. on through the day, and the 8 a. m. value has consistently been the high value of the day. We had another group started at 9 a. m., and the 9 a. m. value was the high value for the day. There is, as far as we have observed, no effect of food intake on the values that are obtained.

The observation of very low values in the early newborn period is a most interesting one. This brings up a question upon which we have speculated for a long time. I should like to point out the parallelism between the situation here and that which results immediately after discontinuation of therapy with hormones, either corticotropin or cortisone. In any patient who has received long-term hormone therapy, during the first few days after its discontinuation the circulating levels of the 17-hydroxycorticosteroids are very low, in most cases zero. This occurs regardless of whether corticotropin or cortisone therapy is used. The newborn infant has been exposed to the elevated 17-hydroxycorticosteroid level of his mother, which is suddenly withdrawn from his environment. His own adrenals have not been working, and his pituitary, perhaps, has been inhibited from secreting corticotropin because of the high concentration of circulating steroids of the mother. Upon withdrawal of the mother's steroids, it seems logical that he should react in a fashion quite similar to the patient for whom hormone therapy has just been discontinued.

Dr. Lytt Gardner, Syracuse, N. Y.: I should like to say "Amen" also to Dr. Klein's important observation of the values in newborn infants. I think this adds one more brick to the structure which Dr. Klein originally began building a few years ago, when he postulated that the newborn infant has some remarkable similarities metabolically to the child with congenital adrenal hyperplasia (*J. Clin. Invest.* **30**:*318* [*March*] *1951*).

Dr. Robert Klein, Pittsburgh: There are a lot of questions. I think we will try to answer some of them now. Others will be explained later when we go into this problem again from another point of view.

In answer to Dr. Ely, we have eosinophile counts on a scattering of our patient with infection. They were all low, as would be expected.

We have no eosinophile counts on these particular newborn infants. As is known, the eosinophile count of the newborn infant starts out at fairly low levels, then rises, and along about the seventh day begins to fall again to normal levels. During this time, he is less responsive to corticotropin as measured by eosinophile response, but I think that most people would agree that if enough corticotropin is given, he will respond. I think the best demonstration of the hypothesis that the adrenal has not been stimulated by corticotropin because the newborn pituitary has been suppressed by the excess maternal steroid is the work of Jailer, who showed that his immature rats and newborn rats had very little corticotropin in their pituitaries. In the course of the first week of life he could demonstrate an increasing amount of corticotropin, and this paralleled the changes that we have reported in children and that have been reported from Montreal.

As far as repeating studies on the same patients, we have not done so. I think Dr. Kelley indicated that his group, Dr. Nelson, Dr. Samuels, and people working with the children, have pretty good figures, some of which have already been published.

We have repeated levels on seven out of nine days on one medical student who volunteered to give blood himself, and had fair agreement. However, in the results obtained, actually, from the investigators, over a period of several months, there was considerable variation within the normal range.

We have nothing on body temperature.

The question of sick newborn infants was raised. I wish I could answer that. Any time the interns see me coming and they have a sick infant, they hide it. They are afraid that the additional 25 cc. of blood is going to throw him over the precipice.

If I may hazard a speculation, I would assume that a sick newborn infant will have a high level. We have the first 20 cc. of blood from two exchange transfusions in patients with erythroblastosis, and perhaps you may consider those sick infants. They had no measurable 17-hydroxycorticosterone-like substance.

I cannot answer Dr. Bongiovanni's very important objections to the method. They certainly exist.

I think one thing might be reemphasized as far as the infections go. Dr. Kelley mentioned a great variation in the normal. Our lowest level that we presented with meningitis was 45.

An Experience with Vaccination Against Influenza B in 1952 Using Monovalent Vaccine. Dr. A. V. Hennessy, Dr. Elva Minuse, Dr. F. M. Davenport, and Dr. T. Francis Jr., Ann Arbor, Mich.

An epidemic of influenza B occurred in a vaccinated and control population of children and adolescents three and one-half months after administration of a monovalent vaccine containing only the Lee strain of Type B virus. The incidence rate was significantly higher in the younger children than in the older ones. The cases in both the vaccinated and the control group occurred predominantly in those who had low antibody levels. The influenza virus, Type B strain, isolated during the epidemic was shown to be antigenically different from the Lee strain used in the vaccine.

That a significant protection against influenza B was conferred by vaccination was clearly demonstrated, the observed protective ratio being 2.7 to 1. The sera of the cases arising in the B-vaccinated group had acute-phase antibody contents to Type B virus not markedly different from those of the control case. Although the vaccine had been known to have given a good serologic response at two weeks, by six and one-half months after vaccination a marked fall in antibody content had occurred. The cases of influenza B in the vaccinated group appeared, then, to be that part of the group in which the antibody content fell below a protective level and in which the patients were selectively attacked by the disease. Reasons are presented to support the conclusion that this marked fall is the result of lack of previous experience, a function of age, with the antigen.

DISCUSSION

Dr. Harold Ginsberg, Cleveland: I should merely like to ask the speaker if the initial titers of the immunized group that did not get influenza were any higher than those of the group that did.

Dr. A. V. Hennessy, Michigan: There were only three illnesses during the epidemic period in the vaccinated group not proved to be influenza. These persons had high acute titers. Judging from the titers from a six-and-one-half-month sample of the group who had had no evidence of influenza, the titers of the vaccinated group which did not get influenza were higher than the acute titers of the cases.

The Comparative Effects of Fructose and Glucose in the Diet of Alloxan-Diabetic Rats. Dr. Herbert P. Sarett and Dr. Lawrence P. Snipper, Evansville, Ind.

Male rats were raised from weaning on a diet of vitamin-free casein, dextrin, corn oil, salts, and vitamins, and after four weeks were given intravenous injections of alloxan (40 mg. per kilogram of body weight). After several weeks, the animals were separated into comparable groups on the basis of the severity of the diabetes, as judged by repeated measurements of water intake and of blood sugar. The rats were placed in individual metabolism cages and received either fructose or glucose in the diet in place of the dextrin. In the rats changed from the dextrin to the fructose diet, marked decreases in water intake, urinary volume, and carbohydrate content were observed, whereas little or no change was found in the animals transferred from the dextrin to the glucose diet. The volume of water intake per gram of food consumed was also much lower in the animals on the fructose diet than in those on the dextrin or glucose diets. The water intake, urinary volume, and carbohydrate content were correlated with the level of blood sugar, but at comparable levels of blood sugar were lower in the rats on the fructose diet than in those on the glucose diet.

When the diets were reversed and the fructose diet was fed to the animals which had been receiving glucose there was a sharp drop in water intake, urinary volume, and carbohydrate content, whereas the reverse shift from the fructose to the glucose diet resulted in an increased water intake, urinary volume, and carbohydrate content. Analysis of the rat tissues after a final period on these diets showed that the per cent of liver glycogen and the weights of the liver, kidneys, and adrenal glands (as per cent of body weight) were correlated with the level of blood sugar.

DISCUSSION

Dr. Solomon Kaplan, Cincinnati: The authors suggest as an explanation for the increased utilization of fructose the fact that fructose entered the carbohydrate cycle without the necessary intervention of insulin.

I should like to ask the authors if they would care to consider another contributing factor. The uptake of glucose by a rat diaphragm is of course dependent on hexokinase activity, while the uptake of fructose is dependent to some extent on fructokinase activity. Now, the hexokinase system is extremely sensitive to changes in pH, whereas fructokinase is quite insensitive to pH's which are within the limits compatible with life.

The rats with alloxan diabetes may well have had acidosis. I wonder if the authors would answer two questions: (1) Did they have measurements of pH of the sera of their rats? 2. Would they consider the possibility that fructose has an increased utilization partly because of the increased resistance of the enzyme system to changes in pH?

Dr. Dwight M. Scott, Philadelphia: I think in connection with the action of insulin on the hexokinase system, the paper given by Dr. Park at the clinical investigation seemed to show that the insulin effect was not on the hexokinase, but on the absorption of glucose into the cell, into the intracellular fluid.

Perhaps the great difference in glycogen which we see in these diabetic animals in the liver might be a reflection of the fact that the glucose is not able to be taken into the cell and therefore is changed into glycogen in the liver.

Dr. Waldo E. Nelson, Philadelphia: We have had a limited experience with fructose in human diabetes. It needs to be recognized that there are species differences in clinical diabetes and that whatever data are secured from animals cannot necessarily be interpreted as being applicable to the human. In general, however, the results we observed in children were similar to those reported here in animals.

We compared the blood levels and the urinary excretions of sugar during and following the intravenous administration of 10% solutions of dextrose and levulose, respectively.

The differences were not great. They were of about the order shown here, namely, an average of about 15 gm. of glucose excreted during a four-hour period of administration of dextrose in contrast to an average excretion of about 10 gm. during the administration of levulose.

From a practical standpoint, I suspect this difference has no significance in the dietary management of the diabetic child. Whether there are any advantages of levulose over dextrose when the sugars are administered intravenously would seem to be the question.

The occasions when one would inject sugar intravenously are in the treatment of diabetic acidosis and in other instances when for one reason or another the child cannot take food by mouth. I would speculate that the principal advantage of levulose over dextrose would then be in the more rapid utilization of that portion of the levulose which was metabolized without conversion to glycogen and that there would be no differences in the utilization of the portion of levulose which was converted to glycogen in comparison with the metabolism of dextrose. Such differences apparently exist with or without the administration of insulin. Under no circumstances familiar to me, however, should the administration of insulin be omitted in situations in which the intravenous administration of sugar is indicated, except temporarily in the treatment of insulin shock.

Dr. George M. Guest, Cincinnati: I also was very much interested in the statement that most of the sugar lost in the urine of these diabetic rats fed fructose was glucose. Obviously, there is much conversion of fructose to glucose in the body, but this conversion may differ considerably in different species of animals and in different tissues, such as the blood, the liver, and the isolated rat diaphragm. Contradictory statements may be found in the literature regarding the utilization of fructose by blood cells. Recently, Dr. Bruce Mackler and I observed

that when fructose and glucose were both present in whole blood, incubated, the total sugar disappeared at a nearly constant rate up to the completion of glycolysis. But when separate measurements were made of each sugar, we found that fructose was not broken down at all until all the glucose had disappeared. When the glucose was used up, fructolysis proceeded at the same rate as glucolysis. Apparently there is no fructokinase in blood, and fructose is phosphorylated by hexokinase only if no glucose is present. Thus, in the competition of the enzyme systems of the blood cells, glucose is used preferentially.

I should like to ask if any differences were observed in the two groups of rats in the tendency of ketosis developing. If both groups had a good store of glycogen, I would surmise that ketosis didn't develop, but it is a point that merits inquiry.

Dr. Samuel Spector, Cleveland: I should like to ask one question, whether there was any difference in either weight gain or weight loss in the two groups.

Dr. Herbert P. Sarett, Evansville, Ind.: In reply to Dr. Kaplan's question, we realize that there are differences between fructokinase and hexokinase and that each enzyme system might be differently affected by pH or other conditions. We did not measure the pH of the sera, but we do not believe that the difference between the utilization of fructose and glucose is related solely to any acidosis which may have been present. This also brings us to the answer to Dr. Guest's question, and that is, we were not able to detect acidosis or ketosis in the animals on either of the diets.

We have done a number of studies on normal animals and have noted a marked difference in the utilization of fructose and glucose as measured by the rate and extent of glycogen deposition. This also shows that fructokinase and hexokinase work differently when there is no acidosis.

In regard to Dr. Scott's comment on the insulin acting not on the hexokinase but on the entrance of glucose into the cells, I have no controversy with that. I passed over the question of insulin action very quickly to get to the other points in the paper. The mechanism of insulin action is still a debatable one.

The comments of Dr. Nelson were very interesting in regard to his work on infusion of fructose and glucose. We do not contend at all that our data can be directly transferred to work in humans.

The question by Dr. Spector on weight gain can be answered by saying that the animals on the diet containing fructose gained somewhat more weight than did the animals on the diet containing glucose. I did not mention this in the paper since the difference between these average weight gains was not very great and may not have any significance.

Studies of Pulmonary Function in Cystic Fibrosis of the Pancreas. Dr. John R. West and Paul A. di Sant'Agnese, New York.

Studies of pulmonary function require a degree of cooperation not to be found in young children. Therefore, the six patients studied ranged from 12 to 16 years in age. A diagnosis of cystic fibrosis of the pancreas had been previously established by means of duodenal drainage and other clinical and laboratory criteria at varying ages between 6 months and 10 years.

In all cases the following tests were performed: estimation of the total lung volume, vital capacity, residual volume, and maximum breathing capacity. Pulmonary ventilation was measured at rest, during standard exercise, and during the recovery period thereafter. Arterial oxygen saturation and carbon dioxide tensions of arterial blood were also obtained during each of these periods. The percentage of nitrogen in alveolar air was determined as index of intrapulmonary mixing. A spirogram was performed, and the response to bronchodilator agents studied.

In general, the findings were characterized by increased residual volume and impaired ventilatory capacity with apparent difficulty in moving air rapidly in and out of the lungs rather than by restricted total excursion. There was impaired and uneven distribution of air and blood in the lungs resulting in anoxia and increase in CO_2 tension of the arterial blood. Abnormalities in pulmonary function and in gas exchange were most marked in one of the patients who had suffered from progressive respiratory involvement since the age of 10 months and who died a few months after these studies at the age of 13 years. Surprisingly, pulmonary function was only slightly affected in two patients and virtually normal in another, both of whom had had moderately severe respiratory disease for several years and subsequently improved.

It appeared from the results that bronchial obstruction due to intraluminal factors plays the central role in the respiratory involvement of fibrocystic disease of the pancreas. Bronchial walls are affected only if the secondary infection reaches sufficient severity. In cystic fibrosis of the pancreas it is possible, following improvement, to have virtually normal pulmonary function even after years of respiratory disease.

DISCUSSION

Dr. Robert Kaye, Philadelphia: I would like to compliment the authors on their ambitious study and their very nice delineation of the pathologic physiology of chronic pulmonary emphysema. I would like to ask the authors what methods they used in measuring the subdivision of the lung.

A couple of years ago, Dr. Ward Fowler and I adapted Darling's method for measuring functional residual air of infants during the first few days of life. We used the Lilly nitrogen meter for control of complete elimination of nitrogen. This method does not require cooperation from the patient and is based on calculation of the amount of functioning lung tissue from the quantity of nitrogen collected from the patient and the change in concentration of nitrogen in the expired air.

Another method which has certain value in studying patients with pulmonary emphysema due to cystic fibrosis of the pancreas is the pneumotachographic method which we were able to utilize in a study of Dr. May's and Dr. Schwachman's cystic fibrosis patients some years ago. This method requires little cooperation from the young subjects. One gets a tracing of the rate of air flow, and although the alteration that we recognize in patients with the pulmonary complications of cystic fibrosis is not specific and can be also found in asthmatic patients and patients suffering from emphysema and fibrosis, we think this test has a limited usefulness in picking up early evidence of the beginning of pulmonary obstruction and secondary structural changes.

I was interested in the fact that Dr. West evaluated the bronchodilator drugs, and I would agree with him that they are rarely of much value, but occasionally their effectiveness can be striking in these patients.

Dr. Benjamin Kramer, Brooklyn: There are two points that I want to raise in connection with this condition. One is that there seems to be some special susceptibility of these children to repeated respiratory infection, especially pulmonary, which is responsible for these changes in respiratory function. Now, we do see cases of bronchial infection with fibrosis in children due to Staphylococcus and other germs, but these respond very well to antibiotics and the children usually remain well, whereas these children with cystic fibrosis have a marked tendency toward recurrence and aggravation of their pulmonary lesion.

Another point I want to raise is the fact that the continual use of antibiotics has a certain element of danger, namely, the danger of the growth of resistant organisms and possibly also the development of fungus infections that do not respond to chemotherapy or antibiotics.

Dr. Paul R. Patterson, Albany, N. Y.: The problem of the increased collection of viscid mucus in the bronchi and bronchioles of these children has provoked many physicians to ask us, who see a large number of these patients, why we do not develop or use a medication to liquefy the mucus.

In attempting to evaluate this challenge, I wish to call your attention to an investigation done by Boyd and co-workers on the expectorant action of various drugs.

Using animals, they measured the respiratory-tract-fluid output of the most commonly used expectorants as well as other drugs not known to possess an expectorant action. They found that ammonium chloride increased the output of respiratory-tract fluid by 88%, powdered ipecac 143%, potassium iodide 150%, oil of lemon 240%, terpin hydrate 96%. In addition to many other compounds, the sulfonamides were tested. The action of these drugs is what I wish to draw to your attention. Sulfathiazole increased the respiratory tract fluid to 650% and sulfadiazine to 216%.

If these studies have clinical application, it is worth while noting that sulfathiazole and sulfadiazine are our most useful drugs for expectorant action.

We have used and reported on the use of sulfadiazine along with chlortetracycline (aureomycin) in the treatment of the pulmonary involvement of pancreatic fibrosis. I sincerely believe these two sulfonamides do have expectorant action in children.

It is known that parasympathomimetic drugs are the most effective drugs causing increased secretions of the bronchial tree. Clinically, we note that these children cough up sputum after vomiting, crying, or laughing. Parasympathetic drugs have not been thoroughly investigated as a treatment of these children.

In passing, we should express all of our desires to find a specific mucinase to use which will accept the respiratory mucus as a substrate and depolymerize it. Streptokinase and streptodornase do not work. Aerosol trypsin has an equivical effect.

Finally, I would like to mention that these children have much greater respiratory difficulty on damp or rainy days. In fact, if these children are placed in steam rooms, they are made much worse.

In addition to the aggravation of steam, I would like to point out, without going into the physiological reasons, the fact that pure oxygen administration should be avoided. Paradoxically, CO_2 administration will frequently produce a striking improvement (CO_2 has been shown to liquefy bronchial mucous in vivo).

Antibiotics remain our drugs of choice to combat the infection and the development of bronchiectasis.

DR. CHARLES U. LOWE, Buffalo: I should like to mention one fact about oxygen therapy for patients with fibrosis of the pancreas. These youngsters with high CO_2 content in the blood and with poor ventilation, if given oxygen, usually become considerably worse. I should like to emphasize that it is only of the patients with increase in CO_2 in the blood that I am speaking.

We have, in the last six months, seen two youngsters with fibrosis of the pancreas and advanced pulmonary lesions, as well as CO_2 values as high as 40 mEq. per liter; these patients, when put in oxygen tents, became considerably worse, and one of them died.

The physiological explanation is straightforward. The CO_2 value was elevated in the blood, which narcotizes the central respiratory center and renders it no longer effective. So, anoxia is the major stimulation to respiration. If these patients are deprived of their anoxia by inhaling high concentrations of oxygen, their respiratory exchange promptly decreases, much higher levels of CO_2 develop, and they die.

There is one other point which I should like to bring out, and that concerns the pulmonary pathology. Many people describe the lesion as pulmonary fibrosis, yet it is my impression from pathological examination of the lungs that these patients do not have fibrosis of the lung but have emphysema secondary to bronchial obstruction. I do not believe it appropriate to discuss this disease as if it were a fibrosis of the lung.

DR. JOHN R. WEST, New York: I should like to thank those who discussed the paper, and I will try to answer the questions in order.

In measurement of the lung volumes we used the spirographic method for vital capacity and an open-circuit method for residual volume. Arterial pH was determined in each case after exercise as well as at rest, and arterial pCO_2 was calculated. None of the patients were acutely ill at the time of study, but in Patient 6 the pH was 7.30 at rest as well as after exercise. Other patients, however, seen in the wards when acutely ill, have even more pronounced acidosis.

As far as I know, the excessive chloride excretion in the sweat bears no relation to the carbon dioxide retention occurring as a result of pulmonary disease. The former occurs when there is no carbon dioxide retention.

We agree that these patients present a pattern of pulmonary dysfunction like that seen in pulmonary emphysema. The type of dysfunction seen in the fibrosis, i. e., silicosis, asbestosis, and the like, is quite different.

We also have seen carbon dioxide narcosis in these patients as a result of oxygen therapy. Its occurrence must always be watched for when there is carbon dioxide retention along with anoxia. In one instance we tried to forestall its appearance by using a mechanical respirator in the administration of oxygen, but had little success.

In reply to the last comment, pulmonary dysfunction in this disease is, we think, a result of two factors—the basic disease process and the secondary respiratory infections which occur. Our emphasis upon the latter aspect is due to the fact that in this way we seem to be able to do the most for the patient.

Clinical Trial of a Soluble Pertussis Antigen. Dr. Harriet M. Felton, Galveston, Texas.

A new immunizing agent has been prepared by ethanol extraction of a sonic filtrate of Hemophilus pertussis organisms. The potency of the antigen has been adjusted by the results of agglutinin absorption tests using a standard pertussis vaccine prepared from the same mother batch of organisms. Mouse protection tests using the new antigen have shown the material to be as active as the standard reference vaccine.

Infants under 6 months of age in the well-baby clinics of a small city have been chosen by random selection for the study. Five hundred forty babies have been immunized with either the new antigen or a vaccine prepared from the original pertussis organisms used as the starter for the soluble antigen. The babies all received 0.5 ml. of either the whole-organism vaccine or the soluble antigen once a month for three doses. They then were given two doses of alum-precipitated diphtheria toxoid at the next two visits. Blood samples have been drawn after the second diphtheria injection, approximately two months after the third pertussis injection. Boosters of either material were given 12 months after the first dose. The sera have been tested for agglutinins and will be used in passive protection tests in mice. The mean titer in the babies immunized with the soluble antigen is 1:1,052 as compared to 1:324 in the babies immunized with the standard vaccine.

Each infant has been visited by either a physician or a public health nurse the day after each immunization for the purpose of observing evidence of local or generalized reaction to the immunization. In addition to these data, the babies have been observed during one pertussis season. The case rate in each of the immunized groups has been 0.557 per 1,000 person-months of observation, and 4.900 per 1,000 in a carefully selected unvaccinated control group. These figures indicate that pertussis was 8.8 times more frequent among the nonimmunized children than among either of the two immunized groups.

DISCUSSION

Dr. Aims C. McGuinness, Philadelphia: We have very fine antigens now for immunization against diphtheria and against tetanus, particularly if we can get the A substance out of the tetanus toxoid, which probably can be done fairly easily.

Our pertussis antigens certainly have been effective in immunizing against pertussis; however, as antigens they cannot be compared with the tetanus and diphtheria antigens, and we very much need a noncellular antigen, such as Dr. Felton has described.

Experience over many years with adults, however, has led us to find that 10% of adult males do not respond to pertussis vaccination with whole-organism vaccines. That certainly was borne out again in Dr. Felton's study with her whole-organism vaccine, and it would indicate that here we have a very much better antigen with the noncellular vaccine.

The other difficulty with pertussis vaccination is the problem of reactions. Many of us feel that the severe reactions that develop in the older children following injection with triple antigens quite probably come from the pertussis component of the triple antigens. I feel this is a very important beginning of a study which I hope will give us an antigen which will not only be more free from reaction-producing properties but also be a better immunizing antigen than any currently available.

Dr. William L. Bradford, Rochester, N. Y.: Dr. Felton has clearly demonstrated that this new agent is really antigenic in that it produces a definite agglutinin titer. The agglutinin titer in pertussis is variable, somewhat like that in typhoid fever. It is known to last for six months or longer and then often diminishes until it disappears completely. Yet, the patient remains immune to a second attack in the majority of instances.

I have always been interested in the pertussis agglutinogen (Flossdorf) and urged its preservation when its production was finally discontinued. With this agent, which also was very antigenic, one could perform a skin test and in an immune person obtain a tuberculin-like positive reaction, in a susceptible person, a negative reaction.

Occasionaly, we regarded the skin test as a better indicator of immunity than the agglutinin titer, particularly in infants.

I wonder if Dr. Felton has tested these infants with her antigen, or with pertussis agglutinogen?

May I also inquire if Dr. Felton has information concerning the effect of injection of her antigen upon the lymphocytes?

Dr. Von Hoff, East Orange, N. J.: Some years ago, I followed the leucocyte count on a number of persons who received the pertussis antigen plain, and I was surprised, in the first few cases, to find leucocyte counts of 18,000 and above, and one was 28,000. I cannot recall the exact data.

Consistently there was an increase in leucocytes in all the patients who received the pertussis antigen.

Dr. Harriet M. Felton, Texas: About these titers now, the question always comes up and we have had much fun discussing it one way or the other for a good many years.

None of these babies have been tested with our agglutinogen because we know the material is antigenic, and we probably will, at the end of the study, test out some of these children. We plan to keep these children under observation until their third birthday, and at that time we probably will test a few of them with the agglutinogen to substantiate our other findings.

As far as the lymphocyte response, we have not checked these children, but in some of our earlier work with the development of the purified agglutinogen, you may remember that Dr. Ehrich, at Pennsylvania, did a very careful study with animals, as far as using the different fractions was concerned. There was no lymphocyte response of any sort with the use of the fractions containing just the agglutinogen. As the fractions containing the toxin were introduced into the animals, the lymphocyte response began to go up.

We are hoping to do many things with these children as the study goes along, and I hope that we will have some further information at a later date.

Prolonged Interruption of the Circulation at Extremely Low Body Temperatures in Dogs: An Experimental Surgical Procedure. Dr. John J. Osborn, New York.

This study is concerned with attempts to extend the field of hypothermia down to the temperature range below 15 to 20 C. (59 to 68 F.) which might allow interruption of the circulation for up to an hour to permit prolonged intracardiac surgery.

The immediate hazard of deep hypothermia is ventricular fibrillation. Experiments with anesthetized dogs were carried out with simultaneous observation or recording of blood pressure, respiration, arterial pH, per cent of CO_2 in expired air respiratory minute-volume, and electrocardiographic findings. Dogs subjected to cooling followed a rather constant pattern, consisting of early hyperventilation with coincident alkalosis, followed by hypoventilation with acidosis, followed by ventricular fibrillation. It was possible to prevent the alkalosis and acidosis by manipulation of a positive-pressure respiratory system, and in animals with blood pH so controlled, ventricular fibrillation did not develop. Prevention of the early alkalosis appeared more important than prevention of the acidosis.

A mechanical blood pump and oxygenator was then utilized to induce more rapid cooling by direct cooling of the blood in an extracorporeal circulation. The apparatus is a centrifugal oxygenator of rapid circulation time and low inherent volume. Some specifications are the following: flow rate to 1,000 cc. per minute, inherent volume 100 cc., circulation time 6 to 8 seconds, and hemolysis under 100 mg. per hour. With this apparatus, cooling to 15 C. can be accomplished in dogs in half an hour. Using the apparatus for rapid cooling and then turning it off for an extended period with the animal in cardiac standstill at a body temperature near 13 C. (55.4 F.), it has been possible to demonstrate return of cardiac action and reflexes after interruption of the circulation for one hour. Return of adequate blood pressure and respiration with survival of the animal for several hours after rewarming and detachment from the machine has been obtained after 40 minutes of interruption of the circulation at a blood temperature of 14 C. (57.2 F.). Inducement of a high serum bicarbonate level through production of respiratory acidosis by administration of 7% CO_2 for one hour before the experiment appears to contribute to vigorous revival and absence of cardiac abnormalities.

However, all animals have eventually died in shock several hours after apparent recovery from hypothermia. The characteristics of this late shock are to be investigated. There is evidence from other workers that it is preventable.

DISCUSSION

DR. SAMUEL KAPLAN, Cincinnati: Definitive surgical procedures for gross structural abnormalities of the heart have stimulated interest in methods whereby the opened "bloodless" heart would allow direct visualization of the intracardiac chambers. This problem may be studied by the use of artificial perfusion, hypothermia, or a combination of both of these methods. Dr. James Helmsworth and I have cooperated with Dr. Leland Clark in experimental procedures in dogs where artificial perfusion of the whole animal was successfully maintained for periods of up to two hours. Although we have not used extreme hypothermia in our experiments, about 100 perfusions have been performed at temperatures between 25 and 32 C. (77 and 89.4 F.). During these studies both venae cavae have been temporarily occluded and their contents bypassed to the artificial heart-lung apparatus. After oxygenation of the blood and the removal of an adequate amount of carbon dioxide, the blood has been returned to the arterial system, thus bypassing the heart and lungs. This circumstance allows cardiotomy with direct visualization of the cardiac chambers. In about 20 dogs we were able to inspect the cavities of the right heart, and after partial excision of the septa the chambers of the left heart were accessible. Open cardiotomy raises two major problems, namely, the control of coronary venous return and air embolism. Coronary venous blood can now probably be controlled by direct aspiration, but the question of air embolization still remains partially unsolved.

We have previously reported the use of this apparatus in two patients. The first was in an adult with terminal severe congestive heart failure from cor pulmonale. About one-quarter to one-third of the venous return was oxygenated and recirculated to the right auricle for a period of 75 minutes. There was an immediate improvement in cyanosis and orthopnea, and the passage of blood through the apparatus did not produce hemolysis or affect the formed elements. The second patient was explored for the closure of an auricular septal defect. During open cardiotomy, a bizarre defect between the left ventricle and right atrium was encountered. This defect was closed with difficulty because of the large amount of coronary venous return. The patient survived for 18 hours after surgery and probably died from the effects of blood loss and, possibly, air embolization.

In our experimental work, we have not been troubled by the development of respiratory acidosis and have been able to maintain a normal pH by removal of 3 ml. of carbon dioxide per minute per kilogram of body weight. Finally, although it is true that adult dogs do not commonly survive after exposure to a temperature of 20 C., puppies appear to tolerate even lower temperatures without the development of ventricular fibrillation.

DR. KURT LANGE, New York: Several years ago, we carried out extensive studies on the influence of hypothermia on the heart and the vascular apparatus. In these studies, we came to conclusions which do not fully agree with some of the results reported here today.

With hypothermia, the oxygen dissociation curve shifts to the left. That means that the patients, although he has a fully oxygenated blood supply, cannot give off the oxygen in the cold periphery, and that is the reason why the patients as well as the dogs of Dr. Osborn die. For the duration of hypothermia they are subjected for many hours to real cardiac anoxia. They have a picture of severe myocardial ischemia which is very similar to coronary occlusion, although there is no morphologic occlusion. They have an almost complete cardiac anoxia for the time their body temperature is lowered.

There is a means, however, by which one can shift the oxygen dissociation curve to the right, and this is acidification; when you acidify those dogs, bringing the pH down to approximately 7.1, the changes in the electrocardiogram, which during hypothermia are of an anoxic nature, revert completely to normal. The electrocardiogram shows anoxic changes during hypothermia even when the animals are kept on a well-regulated artificial respiration.

I should therefore like to ask Dr. Osborn if he doesn't feel that shifting of the pH to the acid side may rather help than disturb these animals.

DR. EDWARD L. PRATT, New York: I think that these studies have a wide general interest if we look at certain features of them. First, they demonstrate the invaluable aid which the continuous recording of a number of variables is to the investigator who wants to study any complex physiological situation. Without such records he is not able to see the interrelationship of some of these variables, and without it I am sure that there would be many more mysteries than there are on the problem Dr. Osborn discussed.

The thing of general importance is the by-product that comes out of this study, that is, that it emphasizes the very great caution that we, as clinicians, must practice when we rush into some drastic treatment on the basis of having determined one, or perhaps two, abnormal constituents in the serum, leaving out of our therapeutic plan many other equally important disturbances merely because we have not measured these dysfunctions.

DR. J. FRANCIS DAMMANN, Los Angeles: I should like to ask the author whether serum potassium, calcium, magnesium and phosphorus were very carefully checked throughout and whether there was any relationship to changes in pH.

As regards acidifying of blood, I think there is a solid point there. We have noticed in our patients that if we can maintain a higher than usual oxygenation during cooling, perhaps actually getting a higher volume of oxygen into the plasma, that we can reduce the incidence of cardiac arrhythmia. I wonder if oxygenation isn't more important than changes in pH in causing fibrillation.

DR. JOHN J. OSBORN, New York: The comments of all the speakers are so interesting that it is hard for me to speak again afterwards. I think Dr. Kaplan would probably agree with me in not having quite so despondent a view about the present status of oxygenators. I think they are better, perhaps, than has been indicated, and I personally think that there are two or three of them in the country which are good enough that they show, perhaps, better promise than hypothermia for intracardiac surgery.

Dr. Kaplan mentioned coronary flow. In our oxygenator, incidentally, you can suck in blood from the auricle or ventricle from a side arm, and let it go up into the rotating cones, and it doesn't make any difference if you get air, because the air is taken out in the machine. We never have any trouble in losing blood in the incision to the heart. We can always suck it out and put it back in again.

This question of pH raised by Dr. Lange is extremely important and has bothered us a lot. I have worried about the shift of the oxygen association curve. In our dogs, it is evident that acidosis per se does not cause fibrillation. The dogs do all right if you let them get quite acid down to 7.1 or 7.0. However, in our series (about 20 dogs with a statistically valid difference between the groups) in every animal in which we allowed an early alkaline shift, fibrillation followed; on the other hand, dogs have gotten acidotic without fibrillation as long as they were not previously alkaline.

Now, as to whether we would do better or not by keeping the pH low when the animal is very cold, we might very well do better. I just don't know. Yet, if we keep the pH constant throughout at about 7.3, we haven't run into fibrillation and also not into the electrocardiographic changes which occur just before fibrillation.

In reference to the last question about the ions, we have given it a lot of thought and measurement, but we have not found anything to talk about. We have found no consistent shifts in potassium, in calcium, or in sodium. We didn't measure magnesium or phosphorus, and the only serum-electrolyte change constantly associated with fibrillation was a low value for serum bicarbonate in the few minutes or half hour before fibrillation.

Capillary Permeability to Plasma Albumin and Gamma Globulin. DR. D. J. CONWAY, Boston.

The changes in plasma albumin and gamma globulin concentration have been estimated in blood, urine, ascitic fluid, and edema fluid following intravenous infusions of albumin and plasma gamma globulin to children with the nephrotic syndrome. Immunochemical methods for determining albumin and gamma globulin were employed in this study.

Prior to the administration of these proteins the average albumin concentration was 0.33 gm. per 100 cc. in serum, 0.009 gm. per 100 cc. in ascitic fluid, and 0.0054 gm. per 100 cc. in edema fluid. The gamma globulin concentration was 0.18 gm. per 100 cc. in serum, 0.0065 gm. per 100 cc. in ascitic fluid, and 0.0025 gm. per 100 cc. in edema fluid. Upon the administration of albumin intravenously, the albumin concentration in ascitic fluid rose to a maximum in 6 to 18 hours, whereas the edema-fluid albumin reached a peak concentration only after more than 24 hours. Simultaneous determination revealed little or no increase in capillary permeability to gamma globulin following albumin administration, suggesting the albumin changes to be due to diffusion. When albumin and gamma globulin were infused together in the form of plasma, simultaneous changes were observed in the concentrations of these two proteins.

It is suggested that there is no increase in capillary permeability to proteins in the peripheral circulation, and that the edema fluid turnover of proteins is much slower than in the ascitic fluid. The mechanism of passage of albumin and gamma globulin through the kidney will be discussed.

DISCUSSION

DR. WALLACE W. MCCRORY, Philadelphia: I would like to congratulate the authors for their progress in the study of a subject of fundamental importance to those interested in the pathologic physiology of the nephrotic syndrome.

We have undertaken similar studies, though our approach is quite different. We are utilizing filter-paper electrophoresis to study the pattern of protein in the serum, urine, and ascitic fluid in nephrosis. Our studies to date confirm the findings reported here in finding all of the serum proteins present in ascitic fluid, but in much lower concentration than in serum. The striking difference between urine and plasma in such subjects has been previously described, that is the high concentration in urine of albumin. This approach to the study of the mechanisms of membrane permeability to protein offers great promise. The tentative statement that there is no evidence that a general change in capillary permeability exists, whereas a definite abnormality does exist in glomerular permeability, cannot be accepted without more detailed study. The glomerulus is unique, since both active filtration and diffusion occur simultaneously, whereas passive diffusion is the major factor in capillaries elsewhere in the body. The pattern of the urinary proteins in nephrosis has long suggested, since in albumin the smallest protein molecule predominates, that molecular size is the major determinant of glomerular leakage of protein. More critical study of the renal clearance of the various serum-protein fractions is needed before any comparison of patterns in urine and other body fluids (edema, ascites, and serum) can be critically interpreted in terms of reflecting the state of membrane permeability or the processes affecting it.

DR. DAVID GITLIN, Boston: I don't think there is enough evidence at the moment from this sort of study to answer Dr. McCrory's question. All we can say is, because of the fact that normal values for the plasma-protein composition of normal capillary filtrates are unavailable at present, we cannot detect any gross abnormality of the capillaries in the periphery, either in the skin or in the peritoneal circulation.

As regards this problem with respect to urine, we must remember that the protein in ascitic fluid and edema fluid is not lost to the circulation, whereas it is lost to the circulation in the urine; but to answer Dr. McCrory's question exactly at this point, we need more exact values for normal capillary filtrates than are available.

DR. D. J. CONWAY, Boston: I would agree with Dr. Gitlin's comment as regards Dr. McCrory's question one needs to know more about the mechanism of passage of protein through the glomerulus. The constitution of normal tissue fluid, in particular its protein content, has yet to be accurately determined, and future work is being contemplated to elucidate this aspect.

The Effect of Cortisone upon Certain Protein-Nucleic Acid Components of Liver Cells. DR. CHARLES U. LOWE, Buffalo, and DR. W. LANE WILLIAMS, Minneapolis.

Although cortisone is a clinical tool enjoying wide application, its intermediate biochemical effects are largely unknown. A significant amount of information suggests that it is a catabolic hormone regularly causing an increase in urinary nitrogen. There is evidence to indicate that normally the fabrication of protein, at least in the liver, is intimately associated with and dependent upon nucleic acid metabolism. Hence, studies designed to understand the effects of cortisone on protein metabolism might logically start with an investigation of nucleic acid metabolism. The experiments summarized below were undertaken with this in mind.

After appropriate mechanical and chemical separation, a number of nucleic acid fractions of the liver of cortisone-treated rats were studied both with respect to total nucleic acid content and rate of incorporation of radioactive phosphorus (P^{32}). The former measurement is indicative of the quantity of nucleic acid present, and the latter measurement is related to the rate of synthesis of that nucleic acid. Portions of the liver were also prepared for histochemical examination and studied for protein, ribonucleic acid, and desoxynucleic acid. The results in cortisone-treated animals were compared with those obtained from normal controls.

The differences between the two groups of animals were striking. Treatment with cortisone resulted in the complete dissolution of microsomes and mitochondria. That the disappearance was no artifact was indicated by the observation that on histological examination the normal cytoplasmic basophilia of the cell (sedimentable and mitochondral ribonucleic acid) had disappeared.

The ribonucleic acid in other portions of the cell (soluble ribonucleic acid) had increased both quantitatively and with respect to rate of incorporation of P^{32}.

Evidence available from these experiments supports the hypothesis that conversion of soluble ribonucleic acid to particulate ribonucleic acid is prevented by cortisone administration. Since certain enzymes appear to be dependent upon particulate ribonucleic acid for adequate function, particularly the cytochrome system, the implications regarding the activity of these enzymes in the liver following cortisone treatment are most intriguing.

DISCUSSION

Dr. Robert Good, Minneapolis: I should like to congratulate Dr. Lowe on this beautiful piece of work. There is no question from the data presented that the conclusions, in general, are quite correct.

I should like to take exception to the final point he made—the afterthought concerning the basis of enhanced susceptibility to infection under cortisone treatment. This point regards the basis for susceptibility to infection in cortisone-treated animals and my remarks derive from an entirely different kind of study.

In cortisone-treated animals with the infections which we have studied, events proceed much too rapidly to be accounted for on the basis of failure of antibody production. The cortisone-treated animals establish overwhelming bacterial infections, and profound septicemia develops within a matter of hours after the introduction of streptococci. The same thing would seem to hold for many micro-organisms. This is a situation that develops, I believe, with such extreme rapidity that it is difficult to conceive of its being accounted for on the basis of differences in antibody production.

The data which we have accumulated thus far, some of which I will present later, we feel tend to implicate a deficiency in function of the reticuloendothelial system as the basic difficulty in cortisone-treated animals which are subjected to infection.

Another pertinent point is that animals previously immunized against bacteria do not show increased susceptibility under the influence of cortisone therapy. Consequently, it would seem that cortisone does not interfere with the protection afforded by antibodies when they are present.

Dr. Jack Metcoff, Boston: I should like to compliment Dr. Lowe on what I personally believe is one of the most important contributions within this sphere that I have had an opportunity to hear about in recent years.

I should just like to ask one question. Perhaps he has had an opportunity to prepare some protein-deficient rats; if so, what are the responses in these animals?

Dr. Lytt Gardner, Syracuse, N. Y.: I wonder if Dr. Lowe has given such animals 17-hydroxycorticosterone (Compound F)? Dr. Hildegarde Wilson and colleagues have recently made some studies which indicated that cortisone (Compound E), when administered, is converted to 17-hydroxycorticosterone in the body. The 17-hydroxycorticosterone when given remains intact.

One might therefore predict a difference in the reaction of such animals to cortisone versus 17-hydroxycorticosterone.

Dr. Frederick W. Barnes Jr., Baltimore: I wonder, since these indicated results are very dependent on the meaning of P^{32} uptake, that is, on the method used for measuring increases in ribonucleic acid, if Dr. Lowe could enlarge on the significance of each of the methods and their value in drawing quantitative conclusions with regard to changes both in rate of synthesis and in total content of ribonucleic acid.

Dr. Nathan B. Talbot, Boston: I should like to ask just one question, namely, are these same changes observed when smaller doses of cortisone are used? Stating the question another way, should we look upon these changes as being more of a pharmacologic nature, or can we consider them within the realm of physiology as well?

Dr. Charles U. Lowe, Buffalo: I think I should start off with Dr. Good's question.

I would certainly be out of my field if I ventured any reply as to the nature of infection. However, I do believe that the data presented may indicate some reasons for the known increase in susceptibility to infection of cortisone-treated animals and man.

However, there is certain information which is pertinent. Most important is the fact that in animals pretreated with cortisone, at least rabbits, antibodies do not develop as well as in animals that have not been pretreated with cortisone. It was particularly this idea that I had in mind: If the matrix upon which an antigen is to be deposited is absent, there might well be difficulty in developing an antibody. Recently, Haurowitz has shown that tagged antigens, when injected, go not only to the mitochondria of the liver, but also to the mitochondria of the reticuloendothelium system. I think Dr. Good's experiments might be explained on the assumption that the mitochondria are blocked or interfered with in blockade experiments and dissolved when cortisone is administered.

I cannot explain the fact that this change occurs in 12 hours or 18 hours in untreated animals. That may be a separate problem.

To answer Dr. Metcoff, no, we have not tried these experiments on protein-deficient rats. There is good evidence that protein deficiency removes some of the ribonucleic acid from liver cytoplasm, and last year we presented some evidence concerning this phenomenon. But it does not remove or make unsedimentable mitochondria or microsomes. They certainly are decreased in number, but we can be certain that they are not absent.

We have not tried 11-desoxy-17-hydroxycorticosterone (Compound S), in answer to Dr. Gardner. I think his speculations are most interesting.

Now, Dr. Barnes's question is probably the stickiest and the most difficult to answer in a few minutes. The methods used are, I should say, conventional methods, but many conventional methods are open to question. Recently, the incorporation of P^{32} into nucleic acid fractions has been questioned as an absolute measure of the rate of synthesis of these fractions, since when the tetranucleotides are split into their nucleotide components, the uptake of P^{32} was found to be different in each one. However, I rely upon the fact that in repeated experiments—we have done over 100—as an example in isolating mitochondria, the relative specific activity of P^{32} in rat livers is so close to 0.07% day after day and month after month that it must bear some relationship to mitochondrial synthesis, or to the physiology of that component. But I am aware of the criticisms of these methods, and maybe time will permit us to be more precise in elucidating the way different nucleic acid fractions incorporate tagged phosphorus.

Now as to the stains, I have been told by Dr. Williams, who is responsible for the cytochemistry in this paper, that the gallocyanin chromalum stain at pH 2.5 is a specific one for ribonucleic acid, and both he and Lagerstedt have felt that this is an entirely reliable method.

Now, does it tell you how much ribonucleic acid there is per cell or per field that you see on a slide? Obviously, it is more indicative of the amount per field, since you have a very large cell and have diluted the ribonucleic acid in it.

I think we have to rely on the combination of cytochemistry, sedimenting procedures, and the incorporation of P^{32} for our answer.

Dr. Talbot, I think that the effect of cortisone reported is probably a pharmacological action, but I also believe it bears some relationship to normal physiology.

Studies on the Relation of Mechanical Fragility of Erythrocytes to Physiological Jaundice. Dr. David Yi-Yung Hsia, Dr. Richard B. Goldbloom and Dr. Sydney S. Gellis, Boston.

The mechanical fragility of the erythrocytes of new-born infants is markedly elevated at birth and progressively falls so that it reaches normal adult levels by the fifth or sixth day of life. The rate of fall in mechanical fragility correlates inversely with the rate of rise of serum bilirubin levels. In infants with high mechanical fragility of erythrocytes during the first day, there is in most instances a marked hyperbilirubinemia during the first week of life. In those with a low mechanical fragility of erythrocytes, there is no significant bilirubin elevation.

The data appear to add further evidence to the concept that physiological jaundice occurs not only as a result of functional immaturity of the liver, but also as a result of excessive breakdown of red blood cells. The cells which break down appear to be macrocytes and other non-homogeneous forms present at birth which have previously been shown to have a shorter life span than do normal cells.

DISCUSSION

DR. A. ASHLEY WELCH, Cincinnati: I wish to thank Dr. Hsia, Dr. Goldbloom, and Dr. Gellis for adding an interesting new set of observations in connection with the phenomena of physiologic jaundice. As Dr. Hsia has stated, the accumulated evidence which incriminates immaturity of the liver as an important factor in determining the intensity of jaundice is overwhelming. It is so overwhelming that for many years it obscured what we all knew had to be true, namely, that variations in the amount of blood destroyed during the immediate postnatal period logically had to have some effect on the phenomena. The data just presented seem to show clearly that a relationship does exist between the mechanical fragility of a baby's erythrocytes and the degree of bilirubinemia exhibited. It is not so clear to me, however, that the relationship is necessarily one of cause and effect. It might well be that a common factor concerned with the anatomic integrity of the placenta is involved in determining both fragility of erythrocytes and hepatic maturity.

For my own clarification, I should like to ask the authors how the figures 4.75% for fragility and 6 mg. per 100 cc. for bilirubin were selected for use in constructing the final contingency table.

DR. ALTON GOLDBLOOM, Montreal, Canada: Mr. Chairman, it is now 25 years since Gottlieb and I did this original work on icterus.

It is rather nice to see, and keeping it somewhat in the family, that this work has been continued in Boston through the aegis of Dr. Gellis and his two capable associates.

The demonstration of mechanical fragility of red blood cells, of course, is just another corroboration of what we tried to show by cruder methods years ago. It interested me considerably that the proof of mixed population of red blood cells, forthcoming as it is now, was postulated by us years ago through the simple method of washing the residual cells after hemolysis and then subjecting them again to saline suspensions and finding that those residual cells, after the hemolysis of the other cells, showed normal hemolytic phenomena.

With reference to this so-called overwhelming proof of the maturity of the liver, I should like to ask Dr. Hsia what he thinks of the work of Eastman some years ago, who injected bilirubin into the umbilical vein and studied its clearance time from the blood, found that both in those children who had physiologic icterus and in those who had no visible physiological icterus the disappearance time of bilirubin from the blood was identical, and concluded from that that the liver did not play an important part in the genesis of the icterus and that it was essentially a hemolytic phenomenon and merely a question of its clearance from the blood.

DR. GLADYS J. FASHENA, Dallas, Texas: I should simply like to clarify a point which I might have misunderstood. I get the impression from what Dr. Hsia says that he wants to relate the degree of mechanical fragility to the degree of icterus numerically. In other words, he implies that the more mechanical fragility there is, the more icterus, and the less mechanical fragility, the less icterus.

A couple of years ago, we presented evidence before this society concerning the total red blood cell mass in the newborn infant. It was measured at birth and at the end of one week in individual infants. Although there was considerable variation from one infant to another, there was a tendency for the red blood cell mass to decrease slightly and for the plasma volume to increase. There was no relationship whatever between the maximum height of bilirubin attained during the first week in individual infants and the amount of red blood cell destruction which had occurred.

Also, in a previous publication, we were able to show that the amount of bilirubin in the meconium and in the early stools was inversely proportional to the height of the bilirubinemia. In other words, the higher the bilirubinemia, the less bile pigment was excreted in the stools. So that although the source of the bilirubin is undoubtedly red-blood-cell destruction, the degree of hyperbilirubinemia does not appear, to me at least, to be related to the degree of hemolysis, but to other factors, namely, to hepatic immaturity.

I wonder if Dr. Hsia's results might be interpreted differently? I wonder if the amount of macrocytosis and the degree of hyperbilirubinemia might both be reflections of immaturity and not causally related.

DR. EUGENE KAPLAN, Detroit: In our experience, the mechanical fragility of cord blood from normal infants has always been within the normal range. Did the results recorded on the

first day of life by these authors refer to cord blood or blood drawn from the infant? We have been impressed with the great difficulty in avoiding traumatic hemolysis during withdrawal of venous blood from the newborn.

We have transfused the cord blood of normal infants into normal recipients and have invariably found normal erythrocyte survival. It was therefore gratifying to note that Mollison has recently retracted his earlier impression that neonatal erythrocytes survived as a dual population.

Dr. Carl H. Smith, New York: Dr. Hsia and his co-workers are to be congratulated for demonstrating by still another device that the red blood cells in newborn babies possess an increased mechanical fragility. Whether or not this decreased resistance may be applied directly to explain physiological jaundice is another matter. The blood values in the first days of the newborn period present a problem requiring special consideration. Most studies indicate a fairly steady level of hemoglobin and red blood cell values during the first week of life, perhaps a slight decrease, but no sharp drop as occurs in later weeks. Physiological jaundice has been interpreted as depending more directly on liver dysfunction than on excessive hemolysis. Under these circumstances, increased mechanical fragility reveals laboratory evidence of another property of the red blood cell in the same category as other in vitro tests, such as the resistance to hypotonic solutions of sodium chloride. Whether or not the increased red blood cell fragility reflects a process occurring in the circulation of the newborn baby and contributing to physiological jaundice represents an important concept which awaits more extensive appraisal.

Dr. Thomas R. Boggs Jr., Philadelphia: I was very much interested in Dr. Hsia's paper because during the past year we measured the mechanical fragilities of red blood cells of 24 babies on the first, third, and fifth days of life using the technique described by Shen and co-workers (Shen, S. C.; Castle, W. B., and Fleming, E. M.: Experimental and Clinical Observations on Increased Mechanical Fragility of Erythrocytes, Science **100**:387-389 [Oct. 27] 1944.).

Our results were at variance with Dr. Hsia's.

Our average results, expressed in per cent hemolysis, were 5.7 on the first day, 6.5 on the third day, and 5.5 on the fifth day.

We ran bilirubin determinations on the same specimens of blood on which we ran mechanical fragilities. We could show no correlation between the bilirubin levels and the mechanical fragilities.

Dr. Alfred H. Washburn, Denver: I hesitate to add something more, but since this is a repetition of the controversy that fell on the second paper I gave before the society 25 years ago, it seems well to point out that the controversy is still going merrily on.

I do want to make one comment, which Dr. Fashena has already made and which needs to be stressed. It seems to me the way to shed more light on this controversy is the rather careful and prolonged following of each particular child as an individual. I have not done any recent work on it, but some years ago in following a small group of babies I was unable to get any correlation among the size of the change in the number of cells, the level of bilirubin, the severity of the jaundice, or any of the other factors involved.

I think it is like many other controversies. Both factors are active here. There is the factor of cell destruction and another factor in the maturity of the liver. Perhaps we are dealing with a degree of immaturity of the baby which involves both liver function and many other functions, including the size and fragility of the cells.

Dr. Forrest H. Adams, Los Angeles: It seemed to me that Dr. Goldbloom and Dr. Gottlieb's original paper involved osmotic fragility, rather than mechanical fragility. In view of this fact I wonder whether the present authors have done osmotic fragility studies on the patients reported.

My second question is whether or not the present authors feel that mechanical fragility has an advantage over osmotic fragility and if so in what instances is this true?

Dr. Alfred M. Bongiovanni, Baltimore: I should just like to ask Dr. Hsia one question. Has he run duplicates, and if so, precisely what were the differences in his duplicates?

Dr. David Y. Hsia, Boston: I want to thank the discussers. I am glad I have started some controversy. That is always, I think, healthy at such meetings. There probably hasn't been enough of it until now.

I should like to answer the various discussers. First, Dr. Weech's question as to the basis on which the mechanical fragility and bilirubin levels were selected: The bilirubin level was based on the average level of peak bilirubins seen in any group of babies with physiological jaundice. The mechanical fragility represents the mean of a large group of infants, children, and adults which we have studied.

I don't think it would be fair to base this type of study on the mean of the infants alone, since the infants do have higher levels than children and adults.

To answer Dr. Goldbloom's comment, the Eastman work on the use of injection of bilirubin is a very interesting one. However, it is a well-known fact that Dr. Eastman made his injections using direct bilirubin, the bilirubin which is obtained from Eastman Kodak, and this certainly is not the same material as that which has been implicated in physiological jaundice, since it is known that the measurement of the direct bilirubin is always normal in these infants, and it is only the indirect bilirubin which is elevated. Until we can extract and inject the indirect bilirubin which has been presented by Dr. Najjar's group, we will have difficulty in determining whether there is or isn't a delayed excretion of indirect bilirubin.

In answer to Dr. Fashena's question, I think any measurement of total red blood cell mass is open to some question. I presume by the statement she made that she measured total red blood cell counts. In this age group it would be very difficult to base any type of data on the basis of red blood cell counts alone since they are so variable.

In answer to Dr. Kaplan's question, I have personally talked to Dr. Mollison on the subject of his first paper, which is what many of our theories are based on, and on his subsequent viewpoint outlined in his book he hasn't actually retracted all of his original work. Rather, he still believes that there is an increased destruction of red blood cells during the first few days of life, but his data are not as striking as during his first determination because of problems of technique.

The mechanical fragilities were all determined on venous blood taken in the babies during the first 24 hours of life in the first group, and none of them were taken from the cord blood. It is our feeling that cord-blood determinations are unsatisfactory because it clots too quickly prior to defibrination.

The blood groups of all these babies were followed. There was no evidence of erythroblastosis in any of them.

As to the comment from Dr. Boggs, I cannot agree with his statement that mechanical fragilities do not vary in the first week of life. We have done between 200 and 300 determinations in the first week of life, and the data speak for themselves. There is no question but that the mechanical fragility of erythrocytes is markedly elevated in the first few days of life.

To answer Dr. Adams' question, we did do osmotic fragility determinations on these infants and found the same findings which have been reported in the literature, namely, that some infants had elevations of osmotic fragility and some infants had lower than normal osmotic fragility.

It seems that the mechanical fragilities were the only ones which showed any consistent variations from the normal adults. It is our feeling that mechanical fragilities are especially useful in the diagnosis of certain types of hemolytic anemias.

To answer Dr. Bongiovanni's question, we have run numerous duplicates on these determinations, and none of them have a variation greater than 0.5%.

I think, in conclusion, that the type of comments we have received today are the result of the fact that for 30 years this whole question of physiological jaundice has been a matter of so much dispute. The hemolytic concept has not been definitely demonstrated because of these disputes, and the types of comments which have been made today will undoubtedly continue to be made.

The reason that we presented this type of data was to demonstrate that this is one of the few approaches that can be made toward trying to define the hemolytic theory for physiological jaundice. I think that perhaps the most important point which we have not thought about is the question of why it is that a normal full-term baby should acquire a bilirubin value sometimes up to 10 mg. per 100 cc. Assuming that normal red blood cells are being destroyed at the rate of approximately 1% per day, that would not be sufficient to explain the marked bilirumenia which is characteristic of the first few days of life, even assuming the liver is not functioning

at all. This is especially significant when you consider the fact that much of the bilirubin which is present in the blood stream diffuses into the tissues, as has been demonstrated repeatedly in erythroblastosis. Also, why should the bilirubin all be indirect when jaundice due to liver insufficiency is direct in nature?

That leaves us with only one conclusion, that there is an excess destruction of red blood cells during the first few days and that this excess destruction is what causes this excessive bilirubinemia and that this, in turn, causes physiological jaundice.

It is true that the degree of bilirubinemia is undoubtedly also partly related to the liver. In some babies the livers are more functionally mature, so that they are able to remove the bilirubin. In others that is not the case. That is one of the main reasons why it is difficult to get definitive data, because you have two variables, neither of which you are able to control. However, I think the data do demonstrate that hemolysis does occur in the first week of life, and that is what we set out to prove in the first place.

Unusual Properties of a Virus Isolated from the Spinal Cord of a Child with Fatal Poliomyelitis. Dr. Alex J. Steigman, Dr. U. Pentti Kokko, and Dr. Rosalie J. Silverberg, Louisville.

The spinal cord of a child was studied 17 days after onset of a clinically typical instance of bulbospinal poliomyelitis. Histological examination revealed lesions typical of poliomyelitis. Thalamic inoculation of monkeys with an emulsion of the patient's spinal cord produced no paralysis, while inoculation of monkey testicular roller-tube cultures yielded a virus whose cytopathogenicity for fibroblasts can be distinguished morphologically from that induced by three standard strains of poliomyelitis virus. The agent is not neutralized by any of the three standard prototype poliomyelitis antisera.

A review will be made of the histological sections, and the results in tissue culture and animals and the implications of the findings will be discussed.

DISCUSSION

Dr. Frederick C. Robbins, Cleveland: This is a disturbing development to some of us, since it is quite possible that Dr. Steigman has discovered the first strain of Type 4 poliomyelitis virus. Although Dr. Steigman has been very cautious in his interpretation of whether or not this agent caused the disease that killed the patient, it seems most likely that there is a causal relationship. As has been mentioned before, the definition of a poliomyelitis virus as an agent that will cause characteristic disease and histopathological findings in a monkey is hardly a satisfactory one now that we have an equally or more sensitive host in tissue culture. We may well discover other agents that can be propagated in tissue culture and produce poliomyelitis in man but not in the monkey. Dr. Steigman's agent may be such a virus.

The relationship will have to be established of this agent to the other agents that Dr. Enders' group in Boston and Dr. Melnick and associates in New Haven have found and a similar agent described by Dr. Steigman. Most of these, approximately 20 in all, have been isolated, as Dr. Steigman mentioned, from the stools of patients with nonparalytic disease. However, two of the cases were paralytic and one, a case of Dr. Melnick's, was indistinguishable from poliomyelitis. We isolated such a virus from a patient in whom a sudden transverse myelitis had developed from which he recovered.

Even though one demonstrates the development of antibodies in the serum of a patient to a virus isolated from his stool, this does not prove that the clinical symptoms were necessarily caused by the agent isolated. This is well illustrated by the fact that Coxsackie and poliomyelitis viruses have been isolated from the same fecal specimen, and antibodies to both agents have been shown to develop in the patient's serum.

It is important that more information be accumulated as to the frequency of these unclassified agents, their importance as a cause of disease in man, and their relationships.

Dr. Horace L. Hodes, New York: I should like to ask Dr. Steigman whether he thinks it is possible that he was dealing with spinal-cord changes which were in fact due to poliomyelitis virus which he failed to recover, as often happens, as he said, and that the virus which he isolated was present in the blood contained in the cord tissue.

Dr. Rake, Dr. Shaeffer, and I think we may have run into a similar situation in measles encephalitis. In that instance, measles virus apparently was recovered from the brain, but it is possible that it may have been present there only in the blood contained in the organ.

In this connection, I wonder whether Dr. Steigman would like to tell us more about the rest of the autopsy on this child. For example, were there pulmonary lesions which may have been caused by virus, and was there a viremia, which might account for the presence of the new virus in the way I have suggested?

Dr. Andrew J. Rhodes, Toronto, Canada: I would be inclined to agree with Dr. Robbins that probably the evidence that has been produced is strongly suggestive that this agent was the cause in this case, and I imagine that many people will be looking for such agents in autopsy material in the future.

I think that we will have to do a good deal of education of pathologists who have access to this material, because of the fact that they are not accustomed to submit material to the virus laboratory in an obvious clinical case of this kind. We shall have to work out some system of getting such material if we want to make further observations on viruses of this variety.

Dr. Alex J. Steigman, Louisville: I wish to thank the discussers for raising some interesting questions. With regard to Dr. Hodes' query about the autopsy findings other than acute poliomyelitis, the significant ones were obstructive purulent bronchitis and acute patchy bronchopneumonia consistent with the changes seen in other poliomyelitis patients treated with tracheotomy in a mechanical respirator.

The other question raised by Dr. Hodes was whether or not virus present in the blood could have contaminated the spinal-cord specimen. There is no certain way of eliminating this possibility. The viremia of poliomyelitic infection is, however, of short duration; the postmortem examination of this child was conducted 18 days after the onset of illness.

Dr. Rhodes's comments point up the importance of examining in vitro as many spinal cord specimens as can be suitably collected from patients with fatal cases of poliomyelitis. Strains of poliomyelitis virus have been developed in the laboratory which have virtually lost their capacity to produce paralysis in the monkey. Should such strains exist in nature yet be capable of causing human disease, the only possible means of identification may be in tissue culture.

That the virus described is of human origin and not introduced in the laboratory is suggested not only by the high neutralizing capacity of human gamma globulin, but also by the fact that it is immunologically unrelated to any other virus at present in our laboratory, which includes all the known poliomyelitis viruses and the unclassified agents recovered from feces.

Observations on Six Children with Goiter due to Chronic Lymphocytic Thyroiditis.

Dr. Donald Gribetz, Dr. Nathan B. Talbot, and Dr. John D. Crawford, Boston.

It has long been thought that all nontoxic goiters in preadolescent and adolescent children were of the simple colloid variety. In recent years we have had the opportunity of observing 18 girls with nontoxic goiter, 8 of whom have had their goiters studied in detail histologically. Thus far six of this group possessed goiters which on pathological examination exhibited changes consistent with chronic lymphocytic thyroiditis of the Hashimoto type, a finding of interest in view of the supposed extreme rarity of this condition under the age of 20 years. The present report summarizes the clinical and laboratory findings of these patients.

In the patients, 9 to 13 years of age, goiters developed between the 6th to the 10th year of life. Symptoms mentioned by individual patients were mildly suggestive of both hypothyroidism and hyperthyroidism. One patient was short; the remainder were of normal stature. In only one patient were there any local symptoms such as pain, tenderness, or dysphagia.

The thyroid glands of these patients were estimated to be two to four times larger than normal. They were firm and easily outlined and had a granular consistency. In half of the group there was a suggestion of nodules; in a like number, the Delphian node was palpable.

The concentration of protein-bound iodine in serum was low to low-normal in two patients and above normal limits in three. In the latter three instances, the serum butanol-extractable iodine levels, measured by Dr. Evelyn B. Man, were low to low-normal. Radioactive iodine uptake values ranged between 25 to 85% of the tracer dose given; they bore no systematic relation to the other manifestations of this condition.

Because of concern about thyroid carcinoma, the first four patients had subtotal thyroidectomies; in the last two, the diagnosis was made by a needle biopsy technique. Histologic examination revealed varying degrees of parenchymal degeneration as evidenced by small follicles largely devoid of colloid plus extensive lymphocytic infiltration with the formation of germinal centers.

Experience to date with thyroid therapy for this condition, therapy which is said to cause these goiters to shrink in adults, is limited to two of the patients. The first failed to respond to a dose of 110 mg. per square meter of body surface per day and subsequently had a subtotal thyroidectomy. The second patient, in whom diagnosis was by needle biopsy, showed marked diminution in size of her goiter after taking a similar dose of thyroid for eight weeks.

It is concluded that nontoxic goiter in preadolescent and adolescent girls may be due in a significant number of instances to chronic lymphocytic thyroiditis. This condition may be characterized by the presence in the circulation of considerable amounts of protein-bound iodine which is not butanol extractable (thyroxin-like). It also can be productive of Delphian-lymph-node enlargement and thyroid nodularity suggestive of thyroid carcinoma.

DISCUSSION

DR. ARTHUR S. ABT, Durham, N. C.: Are the uptake studies performed at 1 hour, at 24 hours, or when? How do you explain the 85% uptake?

DR. D. GRIBETZ, Boston: In answer to the questions that were raised: First, no therapy of any kind had been given to these children before the radioactive uptake studies were performed; second, these were 48-hour uptake studies, and, third, we cannot explain the 85% uptake value in one of the patients. The most recent patient studied did not have a radioactive iodine study. We are eliminating this procedure in the study of these patients, since it does not appear to yield information of significance in this syndrome.

Renal Function in Anemia. DR. ERIKA BRUCK, Buffalo.

Because chronic anemia can be expected to cause anoxic damage and induce physiologic adjustments in various organs, functions of the kidneys were studied in seven children with Mediterranean anemia, four infants with nutritional anemia, and one with a chronic hemolytic anemia of unknown origin. Our observations contrast with reports in the literature which claim reduction of renal function in children with sickle-cell anemia and in adults with pernicious anemia.

In the 12 patients, glomerular filtration rate, effective renal plasma flow, and blood flow were determined, in some cases repeatedly, both at times of low hematocrit readings and after correction of the anemia. Tubular excretory capacity for paraaminohippurate ($T_{m_{PAH}}$) also was measured in most of the patients.

In the seven patients with Mediterranean anemia, the total renal blood flow was normal or above normal. The effective renal plasma flow and the glomerular filtration rate were greatly elevated (up to twice normal) in five of these seven patients; the only exceptions were the mildest case in the group and a young infant, both of whom had normal functions for their ages. In six of these patients, the $T_{m_{PAH}}$ was measured; in two it was about twice as high as normal, and in the others it was in the normal range.

In the infants with nutritional anemia and the one with a hemolytic anemia, the glomerular filtration rate and the renal plasma flow were usually in the normal range for their ages. The total renal blood flow, accordingly, was below normal at the time the hematocrit reading was low.

In the five patients in whom clearance tests were done both during and after correction of the anemia it was evident that the renal plasma flow and glomerular filtration rate were unchanged when the hematocrit reading was raised as much as to twice or more of its original value; i. e., the renal blood flow is regulated in such a manner that the renal plasma flow remains constant. The flow of red blood cells to the kidneys was very low in all patients with a low hematocrit reading in both groups of cases. In only one test, in a 5-month-old infant with Mediterranean anemia, was it less than one-third of the average normal value.

It is argued that one-third of the normal value of red blood cell flow per minute is probably sufficient to provide the kidneys with a normal amount of oxygen. The kidneys normally account for 6 to 7% of the total oxygen consumption of the body, but they receive 20 to 25% of the

cardiac output. Accordingly, the arteriovenous oxygen difference in the kidney is, on the average, only 1.4 vol. %, or one-third of the value in the mixed blood in the heart. If the oxygen consumption of the kidney did not change in anemia, the kidney would suffer no lack of oxygen if only one-third of the normal volume of red blood cells reached it. The large blood flow through the kidneys under normal conditions seems to be determined not by their need for oxygen but by their need for plasma for the excretory functions.

Impairment of Urinary Concentration in Sickle-Cell Anemia. Dr. Hans W. Kunz, Dr. Gilbert W. Mellin, Dr. M. W. Cheung, and Dr. Edward L. Pratt, New York.

The inability of some patients with sickle-cell anemia to concentrate the urine is mentioned in some textbooks, but apparently no investigation of this peculiarity has been reported.

Fifteen patients with sickle-cell anemia, 4 to 14½ years of age, 13 Negroes and 2 Puerto Ricans, 11 boys and 4 girls, were studied in this regard. None were in crisis, and none had been given a transfusion immediately before this study.

The urinary specific gravity was determined after 12 hours of water deprivation plus a subcutaneous injection of 10 units of vassopressin injection (Pitressin) equivalent to 10 U. S. P. posteriar pituitary units. Fourteen of the 15 patients failed to concentrate the urine above 1.016. These findings suggested that a defect in urinary concentration is common in patients with sickle-cell anemia.

An attempt was made to determine any impairment of the osmoreceptor-hypothalamic-posterior pituitary system in addition to the failure of the renal tubules to respond to antidiuretic hormone. The test devised by Hickey and Hare was employed in five patients and three healthy children. All were hydrated orally over a one-hour period. A 2.5% solution of sodium chloride then was infused intravenously over a period of 45 minutes followed 30 minutes later by a subcutaneous administration of 10 units of vasopressin injection. Urine samples were collected every 15 minutes. The volume was measured and the osmolar concentration calculated from the freezing-point depression. All showed a significant antidiuresis and urinary concentration during or after the hypertonic sodium chloride infusion with inconsistent changes after administration of vasopressin injection. This was presumed to indicate the integrity of the osmoreceptor-hypothalamic-posterior pituitary system.

The patients diluted the urine to an average of 113 mOsm. (milliosmoles) per liter, the controls to 63 mOsm. per liter; the patients concentrated the urine to an average of 443 mOsm. per liter and the controls to 658 mOsm. per liter. The difference between maximum and minimum was 330 mOsm. per liter in the patients and 595 mOsm. per liter in the controls.

Although the patients did not achieve as high a urinary concentration as the controls during this test, the significance of this finding is not clear, inasmuch as at least four factors are determinants of the urinary concentration during osmotic diuresis: (1) the glomerular filtration rate, (2) the rate of solute excretion; (3) the extracellular fluid volume, and (4) the concentration of antidiuretic hormone in the blood.

A comparison between water clearance and osmolar clearance during solute loading would probably be more informative than the maximal osmolar concentration.

A similar impairment of urinary concentration is not found in other types of anemia, including those with recurrent hemoglobinemia and those necessitating repeated transfusions.

The cause of the impaired concentration ability is not clear, although changes in the collecting tubules have been seen in sections of kidneys from patients with sickle-cell anemia.

The impairment of urinary concentration in patients with sickle-cell anemia has practical clinical significance. Since the renal water requirement is greater, there is a risk of dehydration, a factor which may precipitate or aggravate crises and thrombotic phenomena. Adequate fluid intake might avoid the complications of sickle-cell anemia.

Demonstration of Impairment of Urinary Concentration Ability, or "Pitressin-Resistance," in Children with Sickle-Cell Anemia. Dr. W. W. McCrory, Dr. N. Goren, and Dr. D. Gornfeld, Philadelphia.

The fact that fixation of urinary specific gravity may at times be found late in the course of sickle-cell anemia has been long recognized. The frequency of this disorder and the factors responsible for it are unknown. Preliminary observations in a group of eight children with

chronic sickle-cell anemia revealed that they failed to produce a urine of high specific gravity (above 1.020) when subjected to 18-hour fluid deprivation. In an attempt to clarify the meaning of this finding, we undertook more elaborate studies of renal function and response to vasopressin injection (Pitressin) during induced water diuresis in such children. The response of patients with renal disease associated with limitation or loss of concentrating ability to vasopressin injection is impaired. Consequently, this response can be compared quantitatively with that of normal children to reveal the degree of abnormality. Subjects included four normal children, six with sickle-cell anemia, and one (18 years old) with Cooley's anemia. Observations were made after a 12-hour fast. Subjects were given an initial water load (15 cc. per kilogram of body weight) by mouth. An infusion of 5% dextrose was then used (3 to 5 cc. per minute) to maintain water diuresis during the remainder of the observation. Collections were obtained by a voiding after a comparison of the response to that obtained with an indwelling catheter revealed no essential difference in cooperative subjects. After the urine flow rose above 7 cc. per minute, 0.1 mouse units of vasopressin injection per kilogram of body weight was administered intravenously. The observation was continued until the urine flow returned to or exceeded the preinjection level. Endogenous creatinine clearance and creatinine urine-plasma ratios were were calculated for each collection period. The vasopressin injection caused a prompt decrease in urine flow in all subjects. The response in the seven patients with anemia was quantitatively decreased in comparison to the normals in every instance, though the degree was variable. In four patients with anemia, the maximal antidiuresis observed was definitely less marked (1.6 to 3.9 ml. per minute) than that observed in the normals (average, 0.9 ml. per minute). The duration was also shorter (20 to 30 minutes) than that observed in the normals (45 to 55 minute). The remaining three patients achieved maximal antidiuresis similar to that seen in normals, but the duration was shorter (20 to 30 minutes). Changes in creatinine urine-plasma ratios varied in the same manner in the two groups. Estimates of solute excretion in three patients and one normal subject as well as urine flow prior to water loading were not significantly different, thus solute excretion does not appear to be important in this response. Changes in glomerular filtration rate, as judged by endogenous creatinine clearances, were not a contributing factor. Measurements of discrete renal function (by clearance techniques, C_{IN}, C_{PAH}, Tm_{PAH}) in four of the children with sickle-cell anemia revealed normal or supernormal values. We conclude that children with chronic sickle-cell anemia have a decreased capacity for renal tubular reabsorption of water. This abnormality results in a limitation of their ability to excrete a urine of high specific gravity even though renal function would otherwise appear to be normal. Further observation will be needed to clarify the significance of this finding.

DISCUSSION

Dr. James N. Ettelldorf, Memphis, Tenn.: Dr. Tuttle and I are particularly happy to hear the reports of Dr. Bruck and Dr. McCrory in that they have corroborated the increases which we have found in renal hemodynamics in these chronic anemias.

We obtained phenomenal increments in hemodynamics in children with sickle-cell anemia. We were originally disturbed with our results to the extent that we had the analytical procedures checked in another laboratory and found them all right. We are happy that other laboratories are now corroborating our findings.

Dr. Smith is collaborating with us in carrying out further studies in adult patients with sickle-cell anemia. We are finding that as these people grow older, the renal hemodynamics apparently do suffer. The glomerular filtration rate seems to be influenced first, then the plasma flow and tubular function. The oldest patient that we have studied so far is a 34-year-old woman, in whom we found the glomerular filtration rate to be 76 cc. per minute, the plasma flow 590 cc. per minute, and the Tm_{PAH} 70 mg. per minute. Apparently this disease does finally hit the kidneys and in all probability produces lesions which result in reduced renal function.

Dr. Jack Metcoff, Boston: I just wonder if any of the authors can tell me whether renal hypertrophy has been observed in patients with severe anemia?

Dr. Henry L. Barnett, New York: I should like to ask Dr. Bruck if measurements of blood volume were made on any of her patients.

In a few observations where we have done clearances before and after transfusions our results have been very much the same, that is, there was no change in the clearances.

In regard to the observations on patients with sickle-cell anemia, this seems to me to be very interesting. By word of mouth, I have heard of several isolated observations which, if they are true—perhaps other people have actually read about them—might make a pretty picture. One of these is that I have been told that when the hemoglobin precipitates into its abnormal form in sickle-cell anemia, there is an extrusion of water from the cell. I have been told also that sickling can be induced by raising the osmolarity of the serum by injecting hypertonic dextrose or any type of hypertonic solution, and the sickling can also be demonstrated in vitro by suspending sickle cells in hypertonic solutions.

If both of these observations are true, and if, as we hear now, patients with sickle-cell anemia cannot concentrate the urine, it fits into a picture in which if insufficient water is given, the osmolarity of the plasma would be increased; water would be drawn out of the cell; the hemoglobin would be precipitated, and the cells would sickle. I would appreciate some more information about this.

As Dancis and others have done with babies with vasopressin-injection-resistant diabetes insipidus, I think it would be interesting to do assays of antidiuretic hormones on the urine of these babies. Dr. Ames also made such measurements after administration of vasopressin injection.

Finally, I think that one would be interested in knowing whether or not these children were sick enough that they were eating poorly and that their total rate of solute excretion was diminished enough that this could have affected their response to vasopression injection.

Dr. Solomon A. Kaplan, Cincinnati: These, of course, are extremely interesting observations. To find a disease in which an active transport mechanism such as the transfer of para-aminohippurate across the tubular cell wall is hyperactive is truly remarkable.

With regard to the method used for testing of the mechanisms of impairment of water concentration, I should like to mention that there is some variability in the responses of individual patients from day to day to injections of water and also of vasopressin injection. These variations are dependent to some extent on the magnitude of the excreted solute load.

In order to quantitate this impairment of water conservation it is advisable to subject the patients to periods of maximum dehydration followed by the intravenous injection of some nonreabsorbable solute such as mannitol, which has proved to be most useful. Determination of the urine osmolarity by measurement of the freezing point before and after loading will then give an index of the concentrating ability of the kidneys.

Dr. Robert Cooke, New Haven, Conn.: Out of ignorance, I would like to ask whether or not some of these findings are similar to the late residuals of lower nephron nephrosis. This question comes up because, following Dr. Barnett's line of reasoning, in the presence of dehydration the release of hemoglobin from sickled cells might well produce lower nephron injury, as demonstrated experimentally and clinically in transfusion reactions.

Dr. Nathan Smith, Philadelphia: In regard to Dr. Barnett's comments, we have determined by freezing points the osmotic activity of the plasma in sickle cells and in red cells by autoclave. He has reported preliminarily that the osmotic activity of the plasma is increased and that of the red blood cells decreased; by measuring this osmotic activity at the time of crisis, it is found that an even greater increase is found in the osmotic activity at the time of crisis, and we have succeeded in some very preliminary observations in inducing crisis by increasing the plasma of extracellular osmoactivity and have some preliminary observations on reducing the extracellular osmoactivity in patients with crisis.

We are, of course, extremely interested in the implications that come from the work reported by these three observers.

Dr. Philip Calcagno, Buffalo: I was merely interested to know whether or not the authors working with sickle-cell disease had related their findings to the number of crises or the number of shock-like pictures that occurred with the patients, and, too, whether or not any clearances were done without the use of intravenously administered materials.

We know that in subcutaneous injections of insulin, perhaps the glomerular filtration rate may not rise as high.

DR. ERICKA BRUCK, Buffalo: Dr. Ettledorf, I was interested in the effect of age on the renal function in anemia, too, and I thought that it might be one of the reasons why we had a difference between the nutritional anemias and Cooley's anemia, because the patients with Cooley's anemia had all had anemia for many years.

I don't know whether there is any renal hypertrophy, Dr. Metcoff. We don't have autopsy reports on kidney weights in Cooley's anemia.

I think the other questions were all directed to the other discussers.

DR. HANS W. KUNZ, New York: In answer to Dr. Metcoff's question about renal hypertrophy, none of our patients died, but we looked through the literature and we didn't find any renal hypertrophy mentioned in patients with sickle-cell anemia.

Dr. Barnett and others mentioned that hyperosmolarity may cause a crisis. During the infusion of 2.5% saline, none of the patients went into crisis, and it may be interesting at this time to mention that one of our patients had the following phenomenon: Whenever that patient was given about a liter or a liter and a half of water to drink, he went into crisis. That means that decreasing the osmolarity seems to precipitate a crisis.

Dr. Cooke postulates that those patients may have lower nephron nephrosis. I think that is just one more speculation of the cause of this phenomenon.

I don't think there is any relation between the number of crises in the patients and this phenomenon. We had one patient just 4 years old with very little of a history. Another patient was about 15 years old and had had many crises; they presented about the same picture.

DR. WALLACE W. MCCRORY, Philadelphia: I will try to answer a few of the many unanswerable questions asked. In regard to Dr. Metcoff's questions as to whether the clearance studies mean that there has been renal hypertrophy in these children with chronic anemia, I believe the studies done on cardiac output in patients with chronic anemia would offer an alternative explanation. Such studies have shown that cardiac output has been found to be increased, even twice normal. In this sense, the increase in renal clearance values could reflect renal hyperemia associated with increased cardiac output. The fact that increases in values for Tm_{PAH} have been observed following infusions of concentrated human serum albumin is also important. A high value for Tm_{PAH} does not in itself mean that renal hypertrophy is present.

In answer to the question about the evidence of pathologic findings in kidneys of such patients, I can only cite the findings in adults dying of other causes after living years with chronic sickle-cell anemia. Vacuolation of the renal tubules and interstitial fibrosis have been reported in such patients. We have no information on the findings in children with this disease. In answer to the question of the contribution of rate of solute excretion, I mentioned the findings in four of these patients in whom measurements of urinary solute excretion were made. The results were essentially similar to those in the normal subjects. We are thus certain that in our studies rate of solute excretion was not a limiting factor. Dr. Kaplan is quite right in pointing out the need for the study of the response of these subjects to solute loading in comparison to normals if we are to define the mechanism of this renal defect. Unfortunately, we have not made such measurements, though we hope to do so later.

In regard to the similarity of renal damage sustained in lower nephron nephrosis, as mentioned by Dr. Cooke, to the disturbance in these patients, I wish to again emphasize that the patients we studied were well and ambulatory and were free of any apparent renal disease. They did not have any other impairment in renal function, and clearance studies revealed supranormal values; consequently, they are not in any way similar to patients with severe renal injuries like lower nephron nephrosis. I presume Dr. Cooke is thinking of the possibility that dehydration and renal leakage of hemoglobin might be responsible for the change in renal function in these children. Since experimental hemoglobinuric nephrosis requires prior dehydration of the animal for production of maximal renal damage, Dr. Cooke has a good possible explanation. Further study would be needed, however, to prove that oliguria and hemoglobinuria occur in these subjects.

(To be concluded)

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Transmission of Radioiodine (I^{131}) to Infants Through Human Maternal Milk. Carl E. Nurnberger and Alys Lipscomb, J.A.M.A. **150**:1398 (Dec. 6) 1952.

Radioactive iodine passes into maternal milk in sufficient quantity to diminish the uptake in the maternal thyroid. This should be considered when investigating the mother's thyroid. It is said, but not proved, that radioactive iodine diagnostic tracer studies may be hazardous to the breast-feeding infant.

Abstractor's Comment.—[Since the half-life of radioactive iodine is only seven days, weaning seems unjustifiable.]

Kimball, Evanston, Ill.

Heat Processing and the Nutritive Value of Milk and Milk Products. Lawrence J. Schroeder, Michael Lacobellis, and Arthur H. Smith, J. Nutrition **49**:549 (April) 1953.

The authors conclude from the results obtained in this investigation under the experimental conditions employed that heat as used in the commercial preparation of evaporated and dried whole milk does not decrease the nutritive value of the protein constituents. Tests on adult dogs have shown that autoclaving whole raw milk at 10 or 15 lb. (4.5 or 6.8 kg.) pressure for 15 or 30 minutes has no detrimental effect on the digestibility, biological value, or nutritive index of the protein. The digestibility and biological value of milk protein do not change if milk is kept in frozen storage for five months.

Fredeen, Kansas City, Mo.

Nitrogen Utilization in Caloric Insufficiency. Warren M. Cox, Rudolph C. Ellingson, and A. J. Mueller, Pediatrics **11**:435 (May) 1953.

To determine whether a portion of ingested protein can be used for tissue growth when insufficient calories were fed, isocaloric and suboptimal amounts of calories in the form of dextrose or as dextrose and protein hydrolysate (Amigen), together with adequate vitamins and minerals, were fed to protein-depleted, partially starved, scalded and normal stock rats. The following conclusions are drawn.

1. The greater the need for protein, the greater is the utilization of ingested nitrogen for new protein synthesis under conditions of caloric limitation. Protein-depleted rats are able to build new protein tissue even when basal energy requirements are not completely supplied.

2. Protein-depleted, partially starved, scalded and stock animals retain or gain more weight when fed adequate or suboptimal quantities of the hydrolysate-dextrose diet than when fed isocaloric quantities of the dextrose diet.

3. Stock animals with no preexisting protein loss and in good nutritive condition do not utilize dietary nitrogen for tissue building when the caloric intake is suboptimal.

4. When the caloric intake is less than that required to meet the estimated basal energy needs, a diet supplying approximately 20% of the calories as proteins supported better growth than those supplying more or less than this amount.

From the Authors' Summary.

CYSTINOSIS. D. A. J. WILLIAMSON, Arch. Dis. Childhood **27**:356 (Aug.) 1952.

The literature relating to cystinosis (cystine storage disease, or Lignac's disease) is reviewed. A case of cystinosis in a girl dying of uremia at the age of 7½ years is described. The diagnosis had been suggested during life by the findings of crystalline deposits in the corneae. Changes in the retinae are also described. A description of the clinical features of the condition is given and the etiology briefly discussed. The treatment of the disorder is of little value and the prognosis hopeless. It is felt that, although cystinosis is undoubtedly very uncommon, cases are probably overlooked because the condition is not borne in mind.

KELLY, Milwaukee.

A CLINICO-PATHOLOGICAL STUDY OF CYSTINOSIS IN TWO SIBLINGS. R. J. K. BROWN, Arch. Dis. Childhood **27**:428 (Oct.) 1952.

Two examples of the rare hereditary disorder of cystinosis are recorded. Necropsy findings are given in the one fatal case. Since the two patients were siblings and the parents first cousins, further evidence in favor of the recessive mode of transmission is provided.

KELLY, Milwaukee.

MALNUTRITION IN THE NATIVE CHILD. J. H. JACKSON, South African M. J. **27**:136 (Feb. 14) 1953.

In view of the nature of the diet and other factors, native children in South Africa suffer from a multiple malnutrition which involves both fat and mineral deficiencies. Jackson feels that degrees of malnutrition exist both generally in the body and locally in individual tissues. Under stress the tissue of the malnourished child may break down locally or generally throughout the body. A deficiency of many factors may be implicated in such a breakdown. Mild malnutrition in the native child is compared with acrodynia in the European, possible similar mineral deficiencies being postulated.

MCGUIGAN, Evanston, Ill.

SOME VERY SEVERE CASES, ONE OF THEM FATAL, OF SPONTANEOUS HYPOGLYCEMIA AND ACETONEMIA. P. NICOLAJ and M. MALOSSI, Clin. Pediat. **34**:708 (Nov.) 1952.

Five children, 9 months to 6 years of age, previously healthy and without warning, went into coma, convulsions, and profuse sweating. The condition in each case was due to hypoglycemia. Aside from acetonemia, no other blood or spinal fluid abnormality was found. Four of the children recovered rapidly after the intravenous injection of dextrose. The fifth child did not receive the necessary treatment in time and died.

HIGGINS, Boston.

Vitamins; Avitaminoses

EXPERIMENTAL MEGALOBLASTIC ANEMIA AND SCURVY IN THE MONKEY: NATURE OF THE RELATION OF ASCORBIC ACID DEFICIENCY TO THE METABOLISM OF FOLIC ACID COMPOUNDS. CHARLES D. MAY, AGNES HAMILTON, and CHARLES T. STEWART, J. Nutrition **49**:121 (Jan.) 1953.

The authors concluded that it seems necessary to seek an explanation other than ascorbic acid deficiency to account for the development of so profound a deficiency of folic acid and folinic acid as occurs in scurvy. It would seem more reasonable to attribute this deficiency to inability to meet an increased requirement for folic acid in scurvy due to greater use or wastage of folic acid because of nonspecific factors operating in scurvy. They believe that scurvy is complicated by a deficiency of folic acid and folinic acid and by megaloblastosis primarily because of nonspecific factors in scurvy which cause increased use or loss of folic acid, rather than because of any specific role of ascorbic acid in the metabolism of folic acid compounds. The diffuse pathology of scurvy may be considered a form of "stress." Infection causes marked depletion of tissue stores of folic acid compounds even when the concentration of ascorbic acid in the tissues is normal.

FREDEEN, Kansas City, Mo.

Effects of Dietary Aureomycin upon the Intestinal Microflora and the Intestinal Synthesis of Vitamin B_{12} in the Rat. K. R. Johansson, G. E. Peterson, and Elliott C. Dick, J. Nutrition **49**:135 (Jan.) 1953.

The purified ration employed by the authors in these studies contained an inadequate amount of methionine, and neither vitamin B_{12} nor chlortetracycline (aureomycin) was able to compensate entirely for the deficiency. When both of the latter factors were added to the basal mixture, a synergistic effect on growth occurred. The inability of supplementation with both B_{12} and chlortetracycline to promote growth at a rate comparable to that observed in those rats fed the stock diet is probably a reflection of the low methionine content of the basal ration. A "methionine-sparing action" by B_{12} and chlortetracycline may be inferred on the basis of their investigation. The inability of chlortetracycline to stimulate the growth of rats fed the natural ration might be interpreted to mean that healthy disease-free animals given access to a well-balanced diet cannot improve their nutritional status if environmental factors are otherwise favorable. The efficiency of assimilation of dietary B_{12} by the host may be increased by chlortetracycline. The results of this investigation indicate that dietary chlortetracycline brings about a rapid and drastic alteration of the intestinal microflora, particularly within the coliform, enterococcus, and Lactobacillus groups of bacteria. There was, however, the rapid development of large numbers of chlortetracycline-resistant bacteria in the gastrointestinal tract.

Fredeen, Kansas City, Mo.

Ariboflavinosis in Infants. T. Porcelli, Pediatria **60**:189 (March-April) 1952.

Twelve infants with symptoms of vitamin B_2 deficiency were seen in Milan in January and February, 1951. The typical fissures of the lips were present in all of the children. Three of them also had a crusting rhinitis, and three had conjunctivitis with photophobia, lacrimation, and fissures of the eyelids.

Four infants had a maculopapular rash over the chin and lips and about the nose. Eleven of them had had bronchopneumonia, and four had gastroenteritis. None were being breast fed. Treatment was with vitamins B and C and brewers' yeast. Three of the children died of bronchopneumonia; autopsy findings on two of them are reported.

Higgins, Boston.

Hygiene; Growth and Nutrition; Public Health

A Training Program for Pediatric Residents in Child Development and Guidance. L. Luzzatti, A. L. Martin, and M. Heinstein, J. Pediat. **41**:86 (July) 1952.

Practicing pediatricians spend 54% of their time in the health supervision of well children, but most hospitals focus their attention on sick children. Resident training programs limited to the ordinary activities of a children's hospital may offer little opportunity to observe the child in his true light, as a member of his family. The authors describe how, with this in mind, they use a child development center and a nursery school to supplement resident training.

Macdonald, Pittsburgh.

An Analysis of 1,617 Consecutive Births. Ethel Barrow, South African M. J. **26**:329 (April 19) 1952.

The author studied the outcome of 1,617 consecutive births in a home for native maternity patients. Patients remained in the home 10 days after delivery or longer in the case of difficult or premature births.

A total of 96.5% of the infants were discharged having been breast fed exclusively. Only four mothers were unable to feed their infants because of complete failure of milk supply. Altogether, 1,206 of the infants weighed over 5½ lb. (2,495 gm.), the average being 7 lb. (3,175 gm.)

There were 1,638 births, including twins. Forty-two were stillborn, and 31 were known to have died in the first 28 days of life. Because of difficulty in follow-up, only the first 10

days of life were considered in the statistics. During this period 27 infants died, a rate of 16.9 per 1,000 live births. Nineteen of these were premature, and 11 of them died within 24 hours. The study revealed that 12% of live births were premature, and 70.4% of the deaths occurred in this group.

Causes of stillbirths and premature labor are discussed.

McGUIGAN, Evanston, Ill.

MATERNAL NURSING AND CARE IN AN ORPHANAGE. G. COLOMBO and E. TAUBER, Minerva pediat. **4**:773 (Sept. 15) 1952.

A study of the case histories of 429 illegitimate infants in a Turin orphanage revealed that the growth, health, and mortality were affected more when the infant was being taken care of by its own mother than when it had breast or artificial feeding. Therefore, the policy of the staff of the institution has been to admit the mother along with the baby, if that is possible.

HIGGINS, Boston.

RELATIONS BETWEEN INDIVIDUAL MORPHOLOGICAL BUILD AND SOMATIC GROWTH. G. DE TONI, Pediatria **61**:1 (Jan.-Feb.) 1953.

One must not evaluate the growth and nutrition of a child merely by his height and weight. It must be remembered that there are different constitutional types, such as those with big bones and those with small bones, the broad child, and the narrow child. Many anthropological measurements are necessary for an accurate judgment of a child's nutritional status.

HIGGINS, Boston.

Prematurity and Congenital Deformities

NATAL AND NEONATAL FACTORS IN PREMATURE INFANT MORTALITY: REPORT OF A TEN-YEAR STUDY. G. R. RUSSELL and W. A. BETTS, J. Pediat. **40**:722 (June) 1952.

This is a statistical study of 1,373 premature infants. The mortality rate for boys was slightly higher than the rate for girls. Most deaths occur in the first 48 hours.

Maternal and obstetric difficulties were bad omens for the infants. Episiotomy and low forceps delivery had a favorable effect on the premature mortality in this study. The mortality rate was high in those cases where general anesthesia or no anesthesia was used. The mortality rate was better in those cases where conduction anesthesia was used.

MACDONALD, Pittsburgh.

REDUCTION OF MORTALITY IN THE PREMATURE NURSERY: INCIDENCE AND CAUSE OF PREMATURITY; ETHNIC, SOCIOECONOMIC, AND OBSTETRIC FACTORS. HARRY BLOCH, HERBERT LIPPSETT, BERNARD REDNER, and DANIEL HIRSCHL, J. Pediat. **41**:300 (Sept.) 1952.

From a study of 960 premature births, the authors conclude that the socioeconomic status of the pregnant mother and the quality of her nutrition are the major influences in determining the maturity of her newborn infant. Ethnic origin, maternal illness, and obstetric conditions are less frequently causative factors.

MACDONALD, Pittsburgh.

FUNCTION OF ADRENAL CORTEX IN PREMATURE INFANTS: I. INFANTS WITHOUT RECOGNIZED DISEASE. JONATHAN T. LANMAN, Pediatrics **11**:120 (Feb.) 1953.

Urinary formaldehydogenic steroid excretions were measured in eight premature infants without recognized disease for varying periods up to 2 months of age. A balance study for sodium, potassium, and nitrogen was carried out in one infant.

Urinary formaldehydogenic steroid excretion did not change measurably during the first 10 days of life and was not significantly different from adult normal values when compared on a surface area basis. Calculations from the data of other investigators indicate that infant values are from one to five times those of adults when compared by surface area. Urinary

formaldehydogenic steroid excretions rose significantly with age when the entire period of study for all infants was included. This rise occurred during the period of fetal cortex involution and is evidence that the fetal zone is not an important source of formaldehydogenic steroids.

The nitrogen- and electrolyte-balance study revealed a loss of potassium in the first two days of life which was disproportionately greater than the loss of nitrogen during the postnatal fasting period. The formaldehydogenic steroid excretion did not change measurably at this time, so that the study does not support the concept of changed adrenal function as a cause for this potassium-nitrogen disproportion. The electrolyte-regulating hormones can, however, vary independently of other adrenal functions. Acute inanition in the neonatal period of fasting is suggested as a possible cause for the disproportion.

From the Author's Summary.

Incidence of Gross Visual Defects Due to Retrolental Fibroplasia. Edward R. Schlesinger and Isabel McCaffrey, Pediatrics **11**:238 (March) 1953.

A study was made of the incidence of gross visual impairment due to retrolental fibroplasia among infants born to residents of New York State, exclusive of New York City, in 1948 and 1949, whose birth certificates indicated birth weights of less than 2,000 gm. and who survived to the age of 4 months. Information was obtained regarding 3,377 infants, or 92.1% of the 3,667 in the group described.

A total of 50 patients with gross visual defects due to retrolental fibroplasia, or an over-all incidence rate of 1.5%, was found. The incidence rates decreased from 15.9% in the birth weight group under 1,000 gm. to 4.3% in the 1,000 to 1,499 gm. group, and 0.7% in the 1,500 to 1,999 gm. group. The infants reported to have the shortest periods of gestation were found to have the highest incidence, the rate in the group with a period of gestation under seven months being 7.6%, as compared with a rate of 0.3% in the group whose gestation period was reported as eight months or more.

Although the numbers are small and the measure of gestation as reported on the birth certificate is open to question, the incidence of the condition within each birth weight group was found to be inversly related to the length of gestation. In the 1,000 to 1,499 gm. birth weight group, for example, an incidence rate of 7.0% was found among the infants with recorded periods of gestation of less than seven months, as contrasted with a rate of 1.9% among those in the gestation periods of eight months or more.

There was no statistically significant difference in the incidence of the condition in the group of infants for whom one or more major complications of the mother's pregnancy was reported when compared with the group of infants on whose birth certificates the statement appeared that no such complication occurred. Among infants weighing less than 1,500 gm. at birth, a statistically significant variation in the incidence of the condition was found in different regions of the state. The incidence rate, adjusted for differences in weight distribution, was found to be 1.7% in boys and 1.2% in girls. The incidence rate among infants born to mothers under 30 years of age was 1.3%, which is not significantly different from the rate of 1.9% among the infants born to mothers 30 years of age or more.

From the Authors' Summary and Conclusions.

Retrolental Fibroplasia. Eirlys Jefferson, Arch. Dis. Childhood **27**:329 (Aug.) 1952.

During the past five years, 56 cases of retrolental fibroplasia have occurred among premature babies in two units in Manchester. A survey of 629 infants has shown that only three cases occurred before 1950.

The early stages of the disease are outlined. Phases suggestive of venous obstruction are illustrated. Support is given to the term "retinopathy of prematurity." On six occasions the early changes of the disease have been noted to regress rapidly when the infant is returned to high tensions of oxygen. Variations in the method of administration of oxygen appear to be closely linked with the incidence of retrolental fibroplasia. It is suggested that retrolental fibroplasia can develop when the tension of oxygen available to the tissue of the premature infant is suddenly lowered.

Kelly, Milwaukee.

A Comparative Study of the Circulating Eosinophil Level in Babies: I. Premature Infants. Joan M. Burrell, Arch. Dis. Childhood **27**:337 (Aug.) 1952.

There is a progressive rise in the eosinophile count from the birth level of zero to a high stable level of circulating eosinophiles. This level varies from 900 to 1,650 eosinophiles per cubic millimeter and was reached in three to five weeks. Infants whose progress was unsatisfactory, and who later died, had a marked eosinopenia. The white blood cell count of 68 infants on the first day averaged 9,400 per cubic millimeter and agrees well with figures quoted in the literature. Twenty-nine infants had an average count of 11,200 per cubic millimeter on the 29th day.

The percentage of circulating eosinophiles in counts done on the day of discharge of this group of premature infants lay between 5 and 12 in 50 of the 75 infants.

Kelly, Milwaukee.

Morquio's Disease. J. D. Whiteside and J. A. Cholmeley, Arch. Dis. Childhood **27**:487 (Oct.) 1952.

The literature of Morquio's disease is reviewed and a description of four cases in a family of eight siblings is recorded. The parents of these children were probably related. Dolichocephaly occurred in two of the patients and in one other child in the family. It is present in 9% of patients with Morquio's disease and is probably an associated hereditary abnormality. Mental defect and an abnormally long palate occurred in all three children with dolichocephaly and were probably secondary to this skull abnormality.

Morquio's disease is a hereditary disease transmitted as a recessive.

Kelly, Milwaukee.

Bonnevie-Ullrich Status. B. Carletti and L. Parenzan, Minerva pediat. **4**:861 (Oct. 31) 1952.

Four children with the Bonnevie-Ullrich status showed the typical findings of this syndrome—pterygium colli, cutis laxa, swelling of the dorsum of the feet, hypertelorism, and depressed nasal tip. None of the children were mentally retarded. The pathogenesis of this condition is discussed together with its similarity to mongolism.

Higgins, Boston.

Embryogenesis of Congenital Malformations of the Rectum and Anus. W. Galluzzi, Minerva pediat. **5**:93 (Feb. 15) 1953.

A new theory is presented as to the embryological basis of certain congenital malformations of the rectum and the anus.

Higgins, Boston.

A Case of Bilateral Bonnevie-Ullrich Syndrome. G. Cocozza, Pediatria **60**:200 (March-April) 1952.

The case of a 3-month-old baby with multiple congenital malformations is reported with autopsy findings. The child had webbing of the skin of the neck, axilla, elbow, and hand (hooking deformity). The feet were clubbed, edematous, angiectatic, and crusted. The Bonnevie-Ullrich syndrome also goes under the name of Turner's syndrome.

Higgins, Boston.

Newborn

Dermatitis Medicamentosa in the Newborn. Margaret M. Scannell, J. E. Rorie, and Cleveland J. White, Illinois M. J. **101**:271 (May) 1952.

Two cases of dermatitis medicamentosa in newborn babies are described. One was due to bromide and the other to phenobarbital.

Barbour, Peoria, Ill.

Early Clamping of the Umbilical Cord During Cesarean Section. Stuart Shelton Stevenson, and Loraine Holman Erhard, J. Pediat. **40**:64 (Jan.) 1952.

Stevenson and Erhard dispute Landau's theory that, because the placenta has not been compressed by uterine contractions, the Caesarean-born infant may face a serious blood loss with fatal shock. Their data indicate that immediate clamping of the umbilical cord during Caesarean section does not result in critical blood loss or fatal shock.

Macdonald, Pittsburgh.

Cephalhematoma Associated with Fracture of the Skull. Norman Kendall and Henry Woloshin, J. Pediat. **41**:125 (Aug.) 1952.

This is a statistical report on 2,774 newborn infants. Sixty-nine, or 2.49%, had cephalhematoma. Of these, 16, or 25%, had a fracture of the parietal bone underlying the cephalhematoma. Only one of these had an associated intracranial hemorrhage. According to these statistics (cephalhematoma) occurs more frequently in the infants of primiparae. The incidence is higher in infants delivered with forceps than those delivered spontaneously. Most of these cephalhematomas occur over the right parietal bone. They are commoner in male than in female infants.

Macdonald, Pittsburgh.

Hemorrhagic Infarction of the Kidneys in Infants: Report of a Unilateral Case in an 8-Day-Old Male Infant with Survival of Infant Following Successful Nephrectomy. Conn L. Milburn, Jr., J. Pediat. **41**:133 (Aug.) 1952.

Milburn reports the case of an 8-day-old infant in whom in the course of an acute infectious illness associated with vomiting, dehydration, metabolic acidosis, and shock, a firm, smooth renal mass developed in the right side. A preoperative diagnosis of hemorrhagic infarction of the right kidney was made, on the basis of the findings of oliguria, hematuria, and the mass in the right flank. Removal of the infarcted kidney was followed for several days by oliguria and azotemia, which was thought to be due to lower nephron nephrosis in the remaining left kidney. This cleared. The infant recovered, but at the age of 4 months, bilateral cataracts of the eyes developed.

Macdonald, Pittsburgh.

Impetigo and Acute Infectious Exfoliative Dermatitis of the Newborn Infant (Ritter's Disease). H. F. Lee, R. B. Wilson, C. E. Brown, and T. P. Reed, J. Pediat. **41**:159 (Aug.) 1952.

The authors report two epidemics of pustular skin infections in their newborn nurseries in a period of six months. The apparent cause was a hemolytic Staphylococcus aureus, and the apparent source, the nasopharynges of attending nurses, physicians, maids, and janitors. The cases ranged in severity from pustular pyoderma to acute fulminating exfoliation (Ritter's disease).

All personnel with nasopharyngeal cultures positive for hemolytic Staph. aureus were excluded from the nurseries. Five per cent sulfathiazole ointment was successfully used as a prophylactic inunction.

Macdonald, Pittsburgh.

The Transfer of Sodium to the Extracellular Space and Cerebrospinal Fluid in a Newborn Infant. L. Woodrow Cox, T. A. Chalmers, and O. Conor Ward, Arch. Dis. Childhood **27**:434 (Oct.) 1952.

An injection of isotonic sodium chloride solution labeled with Na^{24} was given intravenously to an infant with a meningomyelocele. Plasma and cerebrospinal fluid samples were obtained at intervals and the concentrations of Na^{24} assayed. The plasma and cerebrospinal fluid attained equilibrium in four and one-half hours.

Kelly, Milwaukee.

AURICULAR FLUTTER IN A NEWBORN BABY. MURIEL M. MCLEAN, Arch. Dis. Childhood **27**:436 (Oct.) 1952.

A case of auricular flutter in a newborn infant is described. Irregularity of the fetal heart was noted two days before delivery. When digitalis was given in high dosage, the cardiac rhythm became normal.

KELLY, Milwaukee.

THE SIGNIFICANCE OF YELLOW VERNIX IN THE NEWBORN. W. C. TAYLOR, J. A. JAMES and J. L. HENDERSON, Arch. Dis. Childhood **27**:442 (Oct.) 1952.

A series of 37 newborn infants with yellow vernix caseosa not associated with hemolytic disease has been studied in conjunction with a control series.

Significant maternal factors in the series were (1) greater maternal age; (2) prolonged gestation period, with abnormally high birth weight, and (3) increased incidence of abnormal delivery. Significant fetal and neonatal factors were (1) increased incidence of intrauterine fetal distress; (2) increased incidence of neonatal apnea and (3) increased neonatal mortality and morbidity, though the numbers were too small for much significance to be attached to these observations.

It is believed that placental degeneration associated with postmaturity may, by producing fetal anoxia, be the cause of the occurrence of this type of yellow vernix in the newborn infant.

KELLY, Milwaukee.

SCLEREMA NEONATORUM, WITH SPECIAL REFERENCE TO A CASE SUCCESSFULLY TREATED WITH ACTH. C. S. WILLIAMS, South African M. J. **27**:78 (Jan. 24) 1953.

The author discusses a case of sclerema neonatorum which was successfully treated with corticotropin (ACTH).

MCGUIGAN, Evanston, Ill.

FETAL HEART SOUND AND FETAL ASPHYXIA. J. A. ABOLINS, Nord. med. **45**:881 (June 6) 1951.

The author reports a study of 209 cases of fetal asphyxia and of 267 stillborn babies and babies who died in the neonatal period out of a group of 5,030 deliveries. Nearly all babies in whom the fetal sounds were inaudible were stillborn. If the sounds were slow, a high mortality rate was noticed, and very often these infants were asphyctic. If the heart sounds were fast or changeable, the prognosis was more favorable.

WALLGREN, Stockholm, Sweden.

NEONATORUM ASPHYXIA. BENGT J. JONSSON, Nord. med. **46**:1221 (Aug. 15) 1951.

The causes of neonatal asphyxia are reviewed. The clinical picture remains fairly uniform, though the asphyxia itself may be due to a wide variety of causes. In connection with the treatment it is of great importance to try to determine the cause and the pathogenesis. The differential diagnosis of congenital heart disease as an etiological factor is also discussed briefly. The effect of asphyxia on the circulation is also discussed. In some cases of very severe asphyxia lasting over a considerable period there may be evidence of renal injury, as in the syndrome of lower nephron nephrosis. Finally, the late effects of asphyxia are reviewed.

WALLGREN, Stockholm, Sweden.

Acute Infectious Diseases

INFECTIOUS MONONUCLEOSIS COMPLICATED BY ENCEPHALITIS WITH PERMANENT DAMAGE TO THE CENTRAL NERVOUS SYSTEM. SALVATORE A. MOTTO, Illinois M. J. **103**:115 (Feb.) 1953.

A case of infectious mononucleosis with encephalitis is presented in which the patient has permanent damage of the central nervous system as manifested by a persistent elicited horizontal nystagmus and residues of right facial paralysis 12 months after onset of the disease.

BARBOUR, Peoria, Ill.

ACUTE INFECTIOUS LYMPHOCYTOSIS: REPORT OF TWO CASES IN THE SAME FAMILY. HARRIS D. RILEY JR., New England J. Med. **248**:92 (Jan. 15) 1953.

Two cases of acute infectious lymphocytosis occurring almost simultaneously in brothers are described. Both patients showed signs of upper respiratory infections, and the course was not affected by penicillin in one case or by chlortetracyline (aureomycin) in the other. The maximum white blood cell counts were 32,800 and 29,750. The leucocytosis persisted between 19 and 26 days in both cases. Marrow studies in one case revealed only hyperplasia of the lymphoid elements.

Other diseases frequently confused with infectious lymphocytosis were eliminated by appropriate means.

The syndrome of infectious lymphocytosis is reviewed.

WHEELOCK, Denver.

PATHOLOGICAL PHYSIOLOGY IN THE ANEMIA OF KALA-AZAR. C. SALAZAR DE SOUSA, Minerva pediat. **4**:893 (Nov. 15) 1952.

This article gives a summary of the work of Portuguese investigators on the anemia found in patients with kala-azar and then presents the observations and conclusions of the author himself.

The anemia in kala-azar is characterized by (1) a diminished iron content in the blood, (2) marked destruction of the red blood cells, and (3) exhaustion of the bone-marrow cells. These changes occur in spite of the fact that the red cells themselves are not directly attacked by the parasite. Therefore it would appear that the anemia is due to hyperactivity of the spleen.

Splenectomy was therefore done in 38 cases of kala-azar before antimony treatment was begun. The mortality rate in these cases was only 50% as against an expected rate of 100%.

HIGGINS, Boston.

EXANTHEMATOUS MEDITERRANEAN FEVER. L. CARTAGENOVA and A. AGNESE, Pediatria **60**:153 (March-April) 1952.

Exanthematous Mediterranean fever is caused by the Rickettsia conorii, the vector, a tick, being found on various animals, but especially the dog. The disease is more usually found in the country districts, but the 17 cases here reported were in the city of Genoa and its immediate vicinity. The disease usually occurs in the summer and autumn. There is a maculopapular rash, frequently with petechiae, distributed over the body surface, especially on the palms and soles; scars remain after the lesions scab off. There is a diffuse but not marked glandular swelling; the spleen and liver are enlarged. There are fever, headache, muscle and joint pains, and vomiting at the onset of the disease.

In five of the cases, lumbar puncture showed clear fluid under pressure, with a positive Pandy test and many lymphocytes. The differential blood cell count showed a lymphocytosis. In seven of the cases, there were symptoms and x-ray findings of a pulmonary infiltration. The fever and symptoms usually lasted about 15 days; chloramphenicol was found to shorten this by several days.

HIGGINS, Boston.

THE MEGAKARYOCYTE CURVE IN VISCERAL LEISHMANIASIS. A. CROSCA and R. DE LUCA, Pediatria **60**:564 (Nov.-Dec.) 1952.

The megakaryocyte curve indicates the course of the evolution of the platelet-producing cells in the bone marrow. The following seven cells are recognized and listed in individual studies: (1) megakaryoblasts, (2) promegakaryocytes, (3) transitional megakaryocytes, (4) granular megakaryocytes, (5) megakaryocytes with platelets, (6) megakaryocytes in involution, and (7) bare nuclei. In five patients with thrombocytopenia in the course of leishmaniasis, there were found marked diminutions of the number of megakaryocytes in the bone marrow in stages more advanced than the granular megakaryocyte. There is probably a diminition in the proliferation as well as a delayed maturation of the megakaryocytes in leishmaniasis.

HIGGINS, Boston.

Chronic Infectious Diseases

STREPTOMYCIN IN MINIMAL TUBERCULOSIS. ETHEL FLOREY, Am. Rev. Tuber. **65**:547 (May) 1952.

An attempt was made to relate streptomycin therapy in early tuberculosis to duration of illness and convalescence, length of hospital stay, and medical attendant's time. Minimal tuberculosis is defined by the American National Tuberculosis Association in terms of extent seen by roentgenograms (no greater than the space extending from the apex of the lung to the lower border of the second rib) and positive bacteriological evidence. Over a two-year period 19 patients were given at least two courses of streptomycin therapy and bed rest; they were compared with 18 patients treated with bed rest, 17 of whom also had collapse therapy. Results, while not decisive, showed better weight gain, a rise in the hemoglobin value, and less time spent in clinics for the streptomycin group. The latter also showed no spread to the opposite side, and no persistent fluid in the pleural cavity, as compared with three of the control group who showed contralateral spread and four who had persistent fluid. In one case, a highly drug-resistant strain of tubercle bacillus appeared, and in two others a strain with reduced drug sensitivity. After two years, the lesions in seven streptomycin-treated patients and in one of the control group were quiescent. Five patients in each group still had active disease.

ROYCE, San Marino, Calif.

TUBERCULOSIS AND SICKLE-CELL ANEMIA. WILLIAM WEISS and S. O. WAIFE, Am. Rev. Tuber. **65**:735 (June) 1952.

In studies of autopsy material, a higher incidence of pulmonary tuberculosis and more severe involvement were found in patients with concomitant sickle-cell anemia than in the general population. The following explanation was postulated: The pulmonary arterial circulation may be blocked by sickled erythrocytes, and hence the only blood reaching the lung is well-oxygenated bronchial arterial blood. The tubercle bacillus is a strict aerobe, flourishing in this altered-lung-tissue environment.

ROYCE, San Marino, Calif.

TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN. THOMAS L. PERRY, J. Pediat. **40**:687 (June) 1952.

The author reports the cases of 26 infants and children with tuberculous meningitis and 15 additional patients with miliary tuberculosis alone. Arrest of tuberculous meningitis was achieved in seven patients, although but two of these are mentally normal. Miliary tuberculosis was arrested in 14 of 15 patients; 7 are now in good health. Most patients were given additional tuberculostatic drugs. Perry says that until we find a better treatment than streptomycin, more attention should be paid to modifications of therapy designed to prevent the loss of brain substance, so frequently seen in the course of tuberculous meningitis.

MACDONALD, Pittsburgh.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

FURTHER REDUCTIONS IN THE MORTALITY IN ACUTE APPENDICITIS IN CHILDREN. SAMUEL MCLANAHAN, Ann. Surg. **131**:853 (June) 1950.

The mortality rates from acute appendicitis generally have been declining more and more rapidly during the past 15 years.

The author presents the results of clinical study extending over 16 years and including among the patients 823 children under 13 years of age with microscopically proved appendicitis. The younger children had the disease less frequently, yet had it in more complicated form. Eighty-six per cent had acutely inflamed unruptured appendices, while 14% had perforated appendices.

A mortality rate of 0.24% has been achieved for the entire group, a rate of 0.14% for the patients with simple acute appendicitis, and a rate of 0.9% for 111 patients with ruptured appendices. These results have been achieved through emphasis on the following points: (*a*)

a policy of prompt operation; (*b*) adequate preoperative preparation; (*c*) general employment of McBurney's incision; (*d*) removal of the appendix whenever possible, the technique of gentle finger dissection being used in cases of abscess; (*e*) adequate postoperative care, and (*f*) cooperation of surgical and pediatric staffs.

BANTIN, Omaha.

CONGENITAL ATRESIA OF THE SMALL INTESTINE WITH REPORT OF CASES. LON GROVE AND EARL RASMUSSEN, Ann. Surg. **131**:869 (June) 1950.

Fifteen cases of congenital atresia of the small intestine are reported in this series. Five patients were admitted in such poor condition that surgery was not believed indicated. Ten patients were operated upon, with one death. Projectile vomiting was a constant symptom. It usually began on the first day and continued throughout the illness. A roentgenogram of the abdomen is of much value in making the diagnosis. Early diagnosis and early institution of supportive treatment, followed by early operative intervention, are deciding factors in the outcome. Operation should not be delayed longer than is necessary to correct the fluid and electrolyte imbalance and to overcome abdominal distention by the use of the Wangensteen suction. Perforation may occur as early as one day after birth.

BANTIN, Omaha.

SURGICAL SIGNIFICANCE OF ANOMALIES OF INTESTINAL ROTATION. CLARENCE E. GARDNER JR., Ann. Surg. **131**:879 (June) 1950.

Intestinal rotation is the process which converts the position of the intestinal tract of the early embryo from a straight structure suspended on a common dorsal mesentery in the sagittal plane to the position seen in the normal child at birth.

Each of the commoner anomalies that may occur in the three stages of rotation is described. Some of the anomalies may exist without symptoms and be detected only incidentally on roentgenologic examination, at operation, or when a diseased organ, particularly the appendix, is found in an anomalous position. If symptoms occur from the abnormality of rotation and fixation, the usual ones are those of partial or complete intestinal obstruction.

BANTIN, Omaha.

ACUTE APPENDICITIS IN CHILDREN. J. MONTGOMERY DEAVER, Ann. Surg. **136**:243 (Aug.) 1952.

The purpose of this study is to evaluate the role of chemotherapeutic drugs and antibiotic agents in the surgical treatment of acute appendicitis in children. The study is based upon 777 consecutive cases of acute appendicitis from 1930 to 1951.

The author felt that the following factors were responsible for the reduction in mortality: (1) carefully controlled preoperative and postoperative fluid-electrolyte administration; (2) increasing use of the McBurney incision, and (3) routine use of gastroduodenal suction in all cases of peritonitis.

Deaver believes that there is no evidence that the mortality is lowered by the use of chemotherapeutic or antibiotic agents. However, he does feel, although unable to substantiate it by any statistical analysis, that the use of chemotherapeutic and antibiotic agents brings about a lowered morbidity.

BANTIN, Omaha.

INTRATHORACIC DUPLICATIONS OF THE ALIMENTARY TRACT COMMUNICATING WITH THE SMALL INTESTINE. JAMES E. DAVIS and WILLIAM A. BARNES, Ann. Surg. **136**:287 (Aug.) 1952.

A review of the findings in six cases and the detailed description of another case form the basis for the suggestion that intrathoracic duplications of the alimentary tract communicating with the small intestine be added to the list of possible causes of two groups of symptoms and signs in infants and small children.

In one group, respiratory symptoms and signs are produced by pressure of the bulbous intrathoracic portion of the duplication distended with gas and fluid. In the other group,

abdominal pain, gastrointestinal hemorrhage, and anemia result from ulceration of, and hemorrhage from, the gastric mucosa that forms the lining of some of these duplications. X-ray examination establishes the diagnosis.

Operative intervention is the only rational treatment. Of the seven patients, two died in the immediate postoperative period and the remaining five have been relieved of symptoms.

BANTIN, Omaha.

ACUTE REGIONAL ENTERITIS IN CHILDREN. ROBERT C. STORRS and ROBERT A. HOLKELMAN, New England J. Med. **248**:320 (Feb. 19) 1953.

The authors present eight cases of acute regional enteritis in children aged 2 to 11 years. The presenting complaint in each simulated that encountered in acute appendicitis, and in all instances exploratory laparotomy and appendectomy were done. All eight patients were studied again at a later date, one in 3 months and the rest from 3 to 13 years after the acute episode. X-rays were obtained in six cases, and these were negative. All patients were completely free of symptoms referable to the gastrointestinal tract, and there was no evidence that the chronic form of regional inflammation of the bowel had ensued.

Surgical removal of the appendix was accompanied by complete recovery without fistula formation, and the authors agree with those who maintain that exploration and appendectomy are the wisest course in the acute form of the disease.

Medical and surgical management of the chronic disease is briefly discussed. This report lends support to Bargan's attitude that in children "acute regional enteritis and chronic regional enteritis are not the same entity."

WHEELOCK, Denver.

INFANTILE DIARRHOEAL DEHYDRATION TREATED WITH ADRENAL CORTICAL HORMONE AND POTASSIUM CHLORIDE. WILLIAM EMDIN, Arch. Dis. Childhood **25**:136 (June) 1950.

This paper reports on the value of adrenal cortex extract and other measures in the treatment of infantile diarrhea with dehydration. Eighty-three cases are reviewed. The degree of dehydration varied; some of the infants had toxic symptoms in addition.

Potassium chloride solution was given orally with good effect. Dietetically, it is recommended that after a short fasting period, milk mixtures of low fat content be offered. The adrenocortical hormone is valuable for treating dehydration and for promoting gain in weight. If intestinal intoxication is present, however, parenteral fluids should be given immediately; later, the adrenal hormone may be administered in order to promote fluid fixation in the body.

KELLY, Milwaukee.

HEPATITIS ASSOCIATED WITH INFANTILE DIARRHOEA. J. WAINWRIGHT, Arch. Dis. Childhood **25**:286 (Sept.) 1950.

A form of hepatitis associated with jaundice and infantile diarrhea is described. The main features are a periportal necrosis of parenchymal cells, with an infiltration of inflammatory cells, and a proliferation of bile canaliculi and fibroblasts. In most cases there is fatty infiltration. The etiology is discussed, and the author expresses the opinion that the hepatitis is caused by a toxin reaching the liver by the blood stream. A possible relationship between this form of hepatitis and congenital biliary cirrhosis is suggested.

KELLY, Milwaukee.

VARIATIONS IN THE PROTEOLYTIC ACTIVITY OF CHILDREN'S STOOLS. JOHN L. EMERY, Arch. Dis. Childhood **27**:260 (June) 1952.

A survey was made of the variation in trypsin activity in meconium and in the stools from normal children and general hospital patients. The tryptic content of meconium appeared to be less than in later childhood. Weaned children had the same mean level of tryptic activity as unweaned children, but there was a greater variation in titer. Approximately 1 in 10 of older children had minimal or no tryptic activity in the stools.

No relationship was found between the tryptic activity of the stools and the consistency, the pH, and the presence of undigested muscle fibers in the stools, and the height, weight, and general nutrition of the children. An increased incidence of trypsin-low stools was found in patients with disorders of the alimentary tract. No increase was seen in children with respiratory infections, cardiovascular diseases, or nephritis. The finding of trypsin-free stools appears to have a higher clinical significance in younger than in older children.

KELLY, Milwaukee.

Psychology and Psychiatry

THE CHALLENGE OF THE "WELL CHILD." ALVIS JOE SCULL, California Med. **77**:285 (Nov.) 1952.

Upon general practitioners and pediatricians falls the responsibility of recognizing and treating most emotional problems in young children. This may be best carried out by the anticipation of expected problems and the advance guidance or counseling of parents. That such problems are of high incidence was indicated in experience at a pediatric clinic where approximately 40% of 7,000 children observed had psychosomatic symptoms.

In order to utilize effectively the limited time available in office practice for well-child care, a physician must have at hand certain basic information on personality development. Many of the normal behavior patterns in children which frequently are misinterpreted as "behavior problems" by parents are presented herein in chart form, divided into critical age periods, to help physicians quickly recognize what is normal and what abnormal in various periods of maximal crisis. Most of the problems of conflict within a child and of conflict between parents and child, it is felt, could be and should be handled at the pediatric level. Some seriously disturbed children need to be referred for psychiatric care. When this is necessary, skillful preparation of the parent and the child by the family physician for referral is most important to successful psychotherapy.

PRYOR, Redwood City, Calif.

SPEECH AND LANGUAGE PROBLEMS OF MENTALLY DEFICIENT CHILDREN. ISAAC W. KARLAN, and MILLICENT STRAZZULA, J. Speech & Hearing Disorders **17**:286 (Sept.) 1952.

Fifty patients from the clinic for retarded children, Jewish Hospital of Brooklyn, were divided into three groups according to their intelligence quotients. There is a definite relationship between the establishment of handedness and the degree of mental retardation. Echolalia, irrelevancy of ideas, perseveration, glibness, and similar communicative behavioral symptoms were seen in many of the cases. Rehabilitation must be aimed at reasonable, realistic goals, with cooperation from the home environment and the educational and social facilities available in the community.

PALMER, Wichita, Kan.

CONGENITAL APHASIA: AN ANATOMICAL AND PHYSIOLOGICAL APPROACH. OSCAR SUGAR, J. Speech & Hearing Disorders **17**:301 (Sept.) 1952.

In order to have congenital aphasia one must postulate early damage to the speech areas of both hemispheres. Motor aphasia can result from damage to the brain other than in Broca's area. The extent of damage necessary to prevent speech development appears to be so considerable that intellectual deficit must be present. Congenital aphasia should refer only to disabilities in speech in children otherwise normal. In the sense of aphasia as it occurs in adults, this implies loss of a learned function, and this type of aphasia does not occur permanently in children. The term "delayed or failure of development of speech" leads to the consideration of intellectual deficit in these children.

PALMER, Wichita, Kan.

THE YOUNG DELINQUENT. B. R. MUKHERJI, Indian J. Pediat. **19**:64 (April) 1952.

A legislative measure known as the Children's Act has been operative in India since 1920, though only in the three largest cities. It was brought about as a result of the industrial

upheaval which caused acute congestion in the large cities, with resultant indifference to the welfare of children. Under the Act, state responsibility for child welfare is shown by the establishment of separate courts for trial of children, institutional training for incorrigibles, and probation officers to supervise delinquents released from custody. The author points out that in Calcutta alone there are probably 50,000 homeless boys who are in need of help and supervision. The work of state-supervised establishments has been a great step forward. Much more must be done, particularly the formation of boys' clubs to attract the homeless boys who are responsible for most of the delinquency.

McGuigan, Evanston, Ill.

Case of Amaurotic Family Idiocy. G. Andrea Piana, Ann. ital. pediat. **5**:189 (June) 1952.

The author describes a case of Tay-Sachs disease in a illegitimate premature child who is now 2½ years old.

From the Author's Summary.

Importance of Isoimmunization in the Pathogenesis of Mongolian Idiocy. R. Corda, Lattante **23**:600 (Oct.) 1952.

Tests on 13 infants with mongolism and their mothers excluded the importance of isoimmunization in the pathogenesis of mongolism, since in only three of the patients were the blood groupings heterospecific.

Higgins, Boston.

Psychologic Disturbance in the Child. Jose F. Diaz, Bol. méd. Hosp. inf., México **7**:359 (June) 1950.

Physical health, emotional equilibrium, and mental health depend, to a large extent, on the manner in which human beings are cared for and led during childhood throughout several stages of development. In the field of child care, studies are made in relation to problems such as feeding, sleep, elimination, and other activities of the child. These are the result of somatic and psychological functions that interrelate harmoniously.

In the area of child pathology, a large number of diseases and medical problems are psychosomatic. The pediatrician is frequently consulted about behavior problems and has to define their somatic or psychologic origin. The most basic aspects of the psychological development of the child are intelligence, emotions, socialization, personality and attitudes. By establishing the intellectual capacity of the child, anxieties and emotional maladjustments arising from the disproportion between what the child is capable of doing and what is demanded of him are prevented.

In order to make a correct interpretation of the incidents in the child's daily life, it is necessary to be informed about his instinctive and emotional development.

To be acquainted with and to accept the personality of a child guarantees his emotional integrity. The attitudes of the physician and of the parents toward the child are fundamental because of the enormous influence that attitudes exert on the child's psychological development.

From the Authors' Summary.

Electroencephalograms in Children with Behavior Disorders. G. Klackenberg and K. A. Melin, Nord. med. **47**:857 (June) 1952.

Forty-five boys, 7 to 15 years of age, without signs of encephalopathy but with behavior disorders were examined electroencephalographically. Twenty-two of them displayed electroencephalographic changes, of which in seven cases there was the question of mild or moderate dysrhythmias. None of the children had had epileptic seizures. As the cause of the changes, the assumption of an organic immaturity of the brain is discussed. The opinion is expressed that children with emotional conflicts of long duration may have an electroencephalographically demonstrable retardation or regression in development.

Wallgren, Stockholm, Sweden.

Diseases of Genitourinary Tract

TREATMENT OF THE NEPHROTIC SYNDROME. EDWARD C. PERSIKE, California Med. **77**:299 (Nov.) 1952.

The nephrotic syndrome may be due to varied causes. It may end fatally or in complete healing. No specific cure exists as yet, and basic treatment is dietary. The degree of edema does not necessarily hold a direct relationship to the status of the kidneys or to the eventual outcome.

PRYOR, Redwood City, Calif.

URETHRAL STENOSIS IN YOUNG GIRLS: A CAUSE OF RECURRENT INFECTION OF THE URINARY TRACT. JOHN W. SCHULTE and GORDON F. WILLIAMS, California Med. **77**:397 (Dec.) 1952.

Recurrent urinary tract infection in young girls may result from unsuspected urethral stenosis. The diagnosis should be considered in the presence of symptoms suggesting obstruction of the lower urinary tract—symptoms such as infrequent voiding and straining on urination, particularly in intervals between bouts of acute febrile illness accompanied by pyuria or bacilluria. If radiopaque medium is retained in the bladder in unusual quantity after voiding at the close of excretory urography, it is suggestive, but not pathognomonic, of urethral stenosis. The diagnosis is established by instrumental calibration of the urethra, with general anesthesia.

Treatment consists in removing the cause by urethral dilatation and administering antibiotics and chemotherapeutic agents to overcome the infection.

PRYOR, Redwood City, Calif.

A CHROMATOGRAPHIC INVESTIGATION OF THE AMINO ACID CONSTITUENTS OF NORMAL URINE. W. H. STEIN, J. Biol. Chem. **201**:45 (March) 1953.

The author has attacked the problem of the amino acid composition of normal human urine through the use of a new method of chromatography employing an ion exchange column of Dowex 50. Over 40 ninhydrin-positive components are present in the urine of normal adult males, and many of these can be positively identified and quantitatively measured. The author compares the values for the various amino acid components obtained by his method with values obtained by other workers using microbiological and other assay methods.

FORBES, Dallas, Texas.

PRIMARY HERPETIC VULVOVAGINITIS: REPORT OF CASE; ISOLATION AND IDENTIFICATION OF HERPES SIMPLEX VIRUS. SAUL KRUGMAN, Pediatrics **9**:585 (May) 1952.

A case of primary herpetic vulvovaginitis is reported. This diagnosis was confirmed by isolation of the virus and demonstration of the development of neutralizing antibodies.

FROM THE AUTHOR'S SUMMARY.

HEREDITARY SEXUAL PRECOCITY. A. WILMOT JACOBSEN and MADGE T. MACKLIN, Pediatrics **9**:682 (June) 1952.

A family is reported in which 27 males were affected with precocious somatic and sexual development. The trait is shown to be dependent upon a sex-limited autosomal gene with a little less than complete penetrance.

FROM THE AUTHORS' SUMMARY.

OXALOSIS: POSSIBLE "INBORN ERROR OF METABOLISM" WITH NEPHROLITHIASIS AND NEPHROCALCINOSIS DUE TO CALCIUM OXALATE AS THE PREDOMINATING FEATURES. L. YING CHOU and W. L. DONOHUE, Pediatrics **10**:660 (Dec.) 1952.

A case is reported of renal failure in a boy subsequent to recurrence of calcium oxalate urinary calculi. The postmortem examination disclosed widespread deposits of calcium oxalate crystals in the tissues. These were particularly prominent in the kidneys and bone marrow.

It is suggested that this is the end-result of an "inborn error of metabolism" in which there was an excessive formation of oxalic acid.

FROM THE AUTHORS' SUMMARY.

RENAL WATER REQUIREMENT OF INFANTS FED EVAPORATED MILK WITH AND WITHOUT ADDED CARBOHYDRATE. EDWARD L. PRATT, and SELMA E. SNYDERMAN, Pediatrics **11**:65 (Jan.) 1953.

The renal water requirement of six rapidly growing small infants on a food mixture composed solely of evaporated milk and water has been compared with the renal water requirement in the same infants on isocaloric feedings of evaporated milk, added carbohydrate, and water. The higher protein and mineral intake of the unmodified milk mixture resulted in an 85% increase in the renal solute load compared with the load from the modified mixture. Although this increase in renal load, and hence renal water requirement, may be of little significance under the usual conditions of water intake and expenditure, the margin of safety against dehydration has been decreased. At the same time, this larger renal solute load may be an important factor in compromising water balance and well-being unless additional water is supplied whenever the usual intake is appreciably decreased, the extrarenal water expenditure is increased, or there is impairment of the ability to produce a concentrated urine.

Thus the practical importance while planning infant feedings of considering properties in addition to purely nutritive factors is emphasized. FROM THE AUTHORS' SUMMARY.

THE TREATMENT OF HYPOSPADIAS. E. LIPWORTH, South African M. J. **26**:453 (May 31) 1952.

The author presents a method of treatment of hypospadias which is applicable to all degrees of the deformity and can be completed before school age. McGUIGAN, Evanston, Ill.

USEFULNESS AND RESULTS OF CLEARANCE TEST IN CHILDREN. H. KALOUD and R. HINRICHS, Ann. Paediat. **179**:278 (Nov.) 1952.

The results of 364 clearance test investigations in healthy toddlers and school children and in others of the same age groups with kidney disorders show no important differences from the values obtained in adults. Therefore this test seems to be the most reliable kidney function test in pediatrics. Until more becomes known about renal physiology and pathology the main value of this method lies in repeated tests when different clearance test methods should be employed simultaneously. Several extrarenal factors should be considered when one reviews the results.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

COMPARATIVE ACTIVITIES OF 17-HYDROXY-11-DESOXYCORTICOSTERONE AND 11-DESOXYCORTICOSTERONE. GEORGES M. C. MASSON, A. C. CORCORAN and IRVINE H. PAGE, Endocrinology **46**:441 (May) 1950.

In adrenalectomized rats, the potency of Compound "S" acetate was found to be approximately one-thirteenth that of desoxycorticosterone. JACOBSEN, Buffalo.

PARATHYROID CONTROL OF SERUM CALCIUM INDEPENDENT OF RENAL MEDIATION. G. S. STEWART and H. F. BOWEN, Endocrinology **48**:568 (May) 1951.

In this study parathyroid gland extract produced within eight hours the normal response of hypercalcemia when administered intravenously to three nephrectomized dogs immediately after the operation. The cumulated data support the view that the parathyroid gland exerts a control over serum calcium that is primarily independent of the kidneys, both in degree and in direction. JACOBSEN, Buffalo.

A MECHANISM FOR THE EOSINOPENIA INDUCED BY CORTISONE AND BY EPINEPHRINE. JACQUES PADAWER and ALBERT S. GORDON, Endocrinology **51**:52 (July) 1952.

Interest has become restimulated in the subject of the eosinophilic leucocyte, largely as a result of recent findings that the numbers of these elements in the peripheral blood are affected sensitively by hormonal factors, particularly those of the adrenal, and by a variety of stressful

states. Explanations have been proposed for the drop in peripheral blood eosinophiles following cortisone or epinephrine administration primarily on the basis of redistribution and destruction of these cells. This paper presents findings which support the hypothesis that the adrenal hormones lead to an augmented destruction of the eosinophilic cell.

JACOBSEN, Buffalo.

THYROID FUNCTION IN NORMAL AND PATHOLOGICAL STATES AS REVEALED BY RADIOACTIVE IODINE STUDIES: I. THYROID I^{131} UPTAKE AND TURNOVER IN EUTHYROID, HYPERTHYROID, AND HYPOTHYROID SUBJECTS. A. STONE FREEDBERG, DAVID L. CHAMOVITZ, and GEORGE S. KURLAND, Metabolism **1**:26 (Jan.) 1952.

The authors report their results obtained in 525 tracer studies in which I^{131} uptake by the thyroid gland was used as an index of thyroid function. In these studies the method of counting differed from the usual procedure in that four Geiger-Müller tubes, connected in a parallel electrical circuit and arranged horizontally around the neck of the subject, were used instead of the conventional single tube. The four-tube technique is claimed to be considerably more accurate as a method of measuring thyroid function than either the single-tube technique or the technique of measurement of I^{131} loss in the urine. Considerably less overlap of values of per cent uptake among normal, hyperthyroid, and hypothyroid groups is encountered in the multiple-tube technique than in studies using other methods. The mean values (and standard deviations) obtained in different groups of patients in this study were as follows: euthyroid 34.6% (10.6), hyperthyroid 71% (13.8), hypothyroid 11.9% (6.3). The average biological half-life of I^{131} was shorter in the hyperthyroid group than in the normal control group, indicating more rapid turnover of administered iodine.

KAPLAN, Cincinnati.

THYROID FUNCTION IN NORMAL AND PATHOLOGICAL STATES AS REVEALED BY RADIOACTIVE IODINE STUDIES: II. FACTORS INFLUENCING THE UPTAKE AND TURNOVER OF I^{131} BY THE THYROID GLAND. A. STONE FREEDBERG, DAVID L. CHAMOVITZ, and GEORGE S. KURLAND, Metabolism **1**:36 (Jan.) 1952.

From their own previous work and that of others the authors describe factors influencing I^{131} uptake and excretion in euthyroid patients. Despite earlier claims to the contrary, they conclude that neither age nor sex has any significant influence on I^{131} metabolism. Average uptake and turn-over are slightly increased in euthyroid patients with diffuse or nontoxic nodular goiters. In subacute thyroiditis uptake may vary from very low to high normal values, while in congestive heart failure uptake tends to be high. The increased uptake in heart failure may be due to reduced elimination by the kidneys, which leads to prolonged exposure of the thyroid gland to administered I^{131}.

The previous administration of tracer doses of I^{131} is not associated with significant alteration in subsequent uptake or turn-over. Administration of large (therapeutic) doses of I^{131}, however, does lower subsequent uptake in euthyroid patients. On the other hand, hyperthyroid patients who have been rendered euthyroid or even hypothyroid by therapeutic doses of I^{131} still show greatly increased uptake. Similar high uptake is found in hyperthyroid patients who have been rendered euthyroid by surgery, propylthiouracil administration, or external irradiation.

The simultaneous administration of carrier (stable) iodide does not affect uptake of I^{131} provided not more than 100 γ of the carrier is administered. After medication with iodine, however, uptake of I^{131} may be blocked for as long as 10 weeks after cessation of therapy. High excretions (low uptake) have also been reported after administration of organic iodine-containing compounds for pyelography and cholecystography. Ingestion of thyroid, potassium thiocyanate, or propylthiouracil also blocs I^{131} intake. The administration of corticotropin is followed by diminished uptake, but cortisone medication may either lower or raise uptake.

KAPLAN, Cincinnati.

PRIMARY AND PITUITARY MYXEDEMA. LOUIS J. SOFFER and J. LESTER GABRILOVE, Metabolism **1**:236 (May) 1952.

The association of gonadal and adrenal cortex insufficiency with hypothyroidism would ordinarily suggest pituitary hypothyroidism. However, recent studies have shown that adrenocortical and gonadal failure may be associated with primary myxedema, and the authors therefore undertook to delineate the diagnostic aids serving to distinguish the two syndromes.

The administration of thyrotropin to a patient with pituitary myxedema results in improvement in the clinical condition, an increase in uptake of radioactive iodine by the thyroid gland, a rise in the basal metabolic rate, and an increase in the concentration of protein-bound iodine in the serum. None of these changes will occur if the patient suffers from primary myxedema. The use of this diagnostic test is not without hazard, for in patients with pituitary myxedema the administration of thyrotropin or thyroid extracts may stimulate the basal metabolic needs to a degree which may exceed the ability of the adrenal cortex to supply "sufficient adrenocortical hormones" and may precipitate adrenal insufficiency.

Blood assays for thyrotropin theoretically would reveal high levels in primary myxedema and low levels in pituitary myxedema. Procedures for these assays are as yet unsatisfactory.

Since exophthalmos has been attributed to the action of thyrotropin on retro-orbital tissues, the association of exophthalmos with hypothyroidism would suggest primary thyroid disease.

The use of corticotropin (ACTH) and epinephrine has not been attended by results which are sufficiently uniform to be of aid in differentiation of the two conditions.

Hypothyroidism associated with a low titer of urinary gonadotropin would suggest the presence of pituitary myxedema, while an increase in excretion would be expected in primary myxedema.

The insulin-dextrose tolerance test is followed by a normal response in primary myxedema and by "hypoglycemia unresponsiveness" in hypopituitarism. A history of thyroidectomy, ingestion of goitrongenic agents, or of thyroid irradiation, suprasellar tumor, etc., may help differentiate the two conditions.

KAPLAN, Cincinnati.

USE OF CORTISONE IN A CASE OF UNSTABLE JUVENILE DIABETES. J. SCHILLER, R. PICARD, and H. CHIMÉNES, Presse méd. **60**:25 (Jan. 12) 1952.

The authors state that cortisone does not induce hyperglycemia as does corticotropin (ACTH) and, therefore, is not contraindicated in the treatment of diabetes. This may be due to the peripheral-tissue action of cortisone.

In support of this thesis, the authors present a case history of an unstable diabetic girl of 12 years. A course of 200 mg. of cortisone acetate was given over 14 days. The course may have been insufficient, since hyperglycemia and glycosuria recurred. Hypoglycemic accidents, however, disappeared.

DAFFINEE, Melrose, Mass.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

MELORHEOSTOSIS LÉRI: REVIEW OF LITERATURE AND REPORT OF A CASE. MILTON B. SPIEGEL and G. H. KAIRANSKY, Am. J. Roentgenol. **64**:789 (Nov.) 1950.

Melorheostosis Léri is a specific syndrome and should be differentiated from other hyperostotic bone conditions with which it may be confused but which have a different prognosis and require some specific treatment. The authors describe the syndrome and discuss its etiologic and clinical aspects.

HARRISON, Oak Park, Ill.

PRESENT TRENDS IN THE TREATMENT OF OSTEOMYELITIS. JAMES K. STACK, Illinois M. J. **102**:355 (Dec.) 1952.

Although the newer treatment methods are concerned primarily with the hematogenous form of osteomyelitis, considerable progress has been made in the treatment of the chronic types by the application of enzyme products used as débridement agents. They, with the antibiotics, have shortened the preparation period of such wounds for reconstruction and have made bone- and skin-grafting procedures possible at an earlier time and with greater assurance of success and ultimate function.

Stack points out that in this antibiotic era, while the morbid processes of osteomyelitis remain the same, the clinical picture and treatment have changed to the extent that it is practically a new disease. Since the original examination of the child is probably done at home or in the outpatient department of a hospital and the diagnosis is not obvious, penicillin is often administered. If penicillin is given in adequate amounts over a proper period of time to a sensitive

organism, sterilization of the blood stream will follow and any incipient bone involvement will be aborted. However, if the dose is inadequate, the improvement in the general clinical picture will be but transient. After administration of the drug has been discontinued, the infection will later flare up and produce the typical disease state. Then, even with the restoration of adequate plasma levels of penicillin, the process has a head start and some degree of bone destruction will be inevitable. In involvement of deeper bones, early recognition will be difficult and widespread destruction may result.

In the newborn and young infant the onset of acute hematogenous osteomyelitis is more insidious. No definite objective findings of systemic infection may be notable. X-rays are perhaps more helpful at an earlier period than in the older age groups.

Accurate diagnosis of the bone involved and of the specific organism are most desirable before treatment is instituted. However, while culture and sensitivity tests are being run, the so-called broad-spectrum antibiotics may be administered.

Staphylococcus aureus is the offending organism in about 85% of the acute cases in children over 6 months of age. Therefore if the disease is suspected, it is desirable to use penicillin or chortetracycline (aureomycin) early and adequately. It is important in preventing acquired resistance in bacteria to use adequate amounts of the specific antibiotic early and often.

Once osteomyelitis has been established, reaching the point of abscess formation and demonstrable bone change, the abscess cavity should be evacuated without entering the bone proper, and solutions of antibiotics instilled locally. In addition, the part should be kept at rest.

BARBOUR, Peoria, Ill.

THE INORGANIC COMPOSITION OF THE HUMAN RIB WITH AND WITHOUT MARROW ELEMENTS. RICHARD H. FOLLIS JR., J. Biol. Chem. **19**:223 (Jan.) 1952.

The author presents analyses for calcium, phosphorus, and carbonate of ribs taken from patients of varying ages. He has also collected data from the literature on this subject. When expressed on a dry fat-free basis, the calcium content does not change appreciably with age, averaging 23.2% when the marrow is included and 25.7% after removal of the marrow. Phosphorus averages 11.7% and shows a slight tendency to decline with increasing age. Carbonate content shows a definite increase as age progresses, from 2.38% in the young fetus to 3.37% in the adult. These data are most welcome in view of the relative lack of systematic information relative to changes in bone composition with age.

FORBES, Dallas, Tex.

OSTEOMYELITIS DUE TO SALMONELLA INFECTION. L. GIACCAI and H. IDRISS, J. Pediat. **41**:73 (July) 1952.

From the Hospital of the American University of Beirut, Lebanon, the authors report a case of osteomyelitis caused by Salmonella enteritidis. The patient, an 11-year-old Arab girl, was first seen five years earlier. Since then the disease had been chronic and metastatic. Chloramphenicol (Chloromycetin) cleared acute symptoms when they appeared, but did not prevent spread of the infection.

The patient had severe anemia that was apparently toxic in nature and not related to antibiotic therapy, since it preceded therapy.

MACDONALD, Pittsburgh.

ORIGIN OF URINARY CREATINE IN PROGRESSIVE MUSCULAR DYSTROPHY. MARCEL ROCHE, JEAN D. BENEDICT, T. F. YÜ, EDWARD J. BIEN, and DEWITT STETTEN JR., Metabolism **1**:13 (Jan.) 1952.

The biochemical defect of creatinuria was studied in a case of progressive muscular dystrophy. Previous work had established that, although the bulk of creatine resides in muscle, it is synthesized in the liver and kidneys from glycine. Creatine in the urine might then originate from one of two sources: First, the muscles might take up normal quantities of the creatine synthesized and this substance might "leak" back into the blood stream and thence find its way into the urine. Second, the muscles might take up only a fraction of the creatine formed by the liver and kidneys, and so the urinary creatine would originate directly from these organs and not be derived from muscle creatine.

The problem of origin of urinary creatine was studied by feeding N^{15}-glycine to a patient with progressive muscular dystrophy. Urinary creatine was found to be considerably richer in N^{15} than was urinary creatinine. This observation was interpreted as indicating that the source of urinary creatine is not the muscles. If urinary creatine were derived from leakage of muscle creatine, then N^{15} should have been equally distributed between creatine and creatinine, since urinary creatinine is derived solely from muscle creatine. The authors conclude that creatinuria in progressive muscular dystrophy is the result of a metabolic defect in which there is failure of the muscles to take up the creatine which is synthesized in normal quantities by the liver and kidneys.

KAPLAN, Cincinnati.

MOBILITY OF THE UPPER CERVICAL SPINE IN HEALTH AND DISEASE. EDWARD H. TOWNSEND JR. and M. LAURENS ROWE, Pediatrics **10**:567 (NOV.) 1952.

Townsend and Rowe present four cases of cervical "subluxation" due to muscle spasm in the cervical region which occurred during an upper respiratory infection. This syndrome differs from the atlantoaxial subluxation. Roentgenograms in the diagnosis of this condition may lead to erroneous diagnosis and treatment.

The normal anatomic and functional ranges of the cervical spine were studied and are discussed. The degree of mobility of the cervical spine is greater than was previously assumed.

FROM THE AUTHORS' SUMMARY.

IMPORTANCE OF EARLY SURGICAL TREATMENT OF CRANIOSYNOSTOSIS: REVIEW OF 36 CASES TREATED DURING THE FIRST SIX MONTHS OF LIFE. ROBERT L. MCLAURIN and DONALD D. MATSON, Pediatrics **10**:637 (Dec.) 1952.

One hundred twenty children have been treated surgically for premature fusion of the cranial sutures in this clinic.

Thirty-six of these were operated on in the first six months of life and constitute the material on which this report is based. These have included 19 instances of sagittal suture closure, 10 with coronal closure, 5 with multiple suture involvement, and 2 of miscellaneous conditions. The marked reduction in incidence and degree of mental retardation, the prevention of visual impairment, and the improvement in cosmetic appearance which can be achieved by recognition and surgical treatment of this lesion in early infancy are emphasized.

The operation of choice in the authors' clinic is linear craniectomy parallel to the suture which is prematurely fused, and insertion of polyethylene film over the bony margins to delay closure. With proper precautions and supportive treatment this type of surgery is well tolerated and the complications are negligible during the first few months of life.

FROM THE AUTHORS' SUMMARY.

CONGENITAL DISLOCATION OF THE HIP: DIAGNOSIS AND NATURAL COURSE. GEORGE W. PLUMMER, Pediatrics **11**:28 (Jan.) 1953.

Physical and roentgen examinations were performed on 227 nine-month-old Japanese infants to discover all cases of congenital dislocation of the hip. Twenty-seven cases were found in which the roentgenograms of the hips were interpreted as abnormal; of these, 15 showed only lack of calcification of the acetabular rim, and the other 12 showed some degree of displacement of the femoral head, in addition to the deficiently calcified acetabulum.

A large percentage of the 27 infants had no physical signs relative to hip deformity.

Repeated examinations at 18 months and 25 months of age demonstrated that all infants with only deficient acetabular calcification and 7 of 12 with some displacement of the femoral head either had had complete healing or showed marked improvement without treatment. Five patients had persistent and aggravated dislocation of the hip.

Limitation of abduction of the flexed thighs is the most consistent and valuable sign of congenital dislocation of the hips, and this is in accord with other investigators' conclusions.

It is proposed that inadequate muscular and ligamentous support to the hip joint is the primary physiologic defect in congenital dislocation of the hip. This view is important in that it

serves to direct attention to the fact that early support to the hip without immobilization of the infant is the most desirable therapy from a physiological standpoint which will prevent deformity of the bony parts of the joint.

From the Author's Summary.

Selective Tendon Transfers for Recurrent Clubfoot. Earnest B. Carpenter and Samuel H. Huff, South. M. J. **46**:220 (March) 1953.

Carpenter and Huff report 18 cases of tendon transfers for recurrence of one or more components of clubfoot in patients who had had previous treatment with wedging casts. Transfer of the anterior tibial tendon to the base of the fifth metatarsal is the procedure recommended by these authors for patients who have recurrence of clubfoot or in whom conservative treatment fails to produce complete correction.

Logan, Rochester, Minn.

Albers-Schönberg Disease. Giacoma Aceta, Riv. clin. pediat. **50**:5 (Jan.) 1952.

The author reports a case of Albers-Schonberg disease and gives a complete description of the clinical and roentgenologic symptomatology. Mild erythroblastosis and acceleration of the curve of maturation of the red cells are noted in the blood.

From the Author's Summary.

Arthrogryposis Multiplex Congenita. Bengt Hagberg, Henrik C. Holmdahl, and Lars Söderhjelm, Nord. med. **47**:357 (March) 1952.

The authors report 15 cases of arthrogryposis multiplex congenita. The localizations of the malformations are tabulated, and the article is illustrated by x-ray pictures and photographs.

Wallgren, Stockholm, Sweden.

Diseases of Eye

A Survey of Methods Used to Reveal Eye Defects in School Children. A. L. Morgan, J. S. Crawford, T. J. Pashley, and J. R. Gaby, Canad. M. A. J. **67**:29 (July) 1952.

Comparison of various vision-testing methods led the authors to conclude that the Snellen charts are the best suited for routine use with school children.

McGuigan, Evanston, Ill.

Cutaneous Diseases; Allergy

Infectious Allergy. Sidney Raffel, California Med. **77**:234 (Oct.) 1952.

The allergic reactivity which accompanies various infectious diseases is different in certain fundamental principles from the allergic disease associated with hypersensitivity to such agents as pollens, dust, and foods. Allergic sensitivity associated with tuberculosis comes about because of the participation of a fatty fraction of the bacillus with another component of the microorganism which is actually the sensitizing substance. The fatty fraction, if isolated from the bacillus, can act with various kinds of sensitizing substances that have nothing to do with tuberculosis to bring about the same kind of hypersensitivity as accompanies tuberculosis. Attempts are being made to learn more about the manner of action of this factor and also to find out whether the organisms of other infectious diseases may have similar chemical constituents that cause allergic disease.

Pryor, Redwood City, Calif.

Moles, Melanomas and Epitheliomas in Children. Nelson Paul Anderson, California Med. **78**:17 (Jan.) 1953.

The management of moles which occur in childhood is important from the standpoint of clinical diagnosis and treatment. Melanomas of both the malignant and the juvenile type are sometimes mistaken for ordinary moles. Malignant epithelial tumors are rare in childhood, as are congenital tumors. There is a possible relationship between congenital defects of various types and childhood neoplasms.

Pryor, Redwood City, Calif.

DISSIMILAR ALLERGIC DISEASE IN IDENTICAL TWINS: A STUDY OF PSYCHOSOMATIC ASPECTS. ROBERT H. CREDE, CHARLES T. CARMAN, ROBERT D. WHALEY, and IRVIN C. SCHUMACHER, California Med. **78**:25 (Jan.) 1953.

Identical twins with bronchial asthma were studied. One had the first attack of the disease in late adolescence; the other, not until he was adult.

The twins were demonstrated by immunologic means to be sensitive to house dust and certain foods. Yet, of itself, the factor of exposure to a known allergen seemed not enough to precipitate clinical allergic reaction in either of them.

It is believed that emotional stress is accompanied by physiologic changes which facilitate increased reactions to antigenic agents that in normal circumstances would not cause clinical disease.

The twins were widely different with regard to emotional development and in their reaction to situations of stress. In both of them allergic manifestations were associated with periods of emotional conflict. The dissimilar clinical manifestations of allergy in these identical twins may be explained by differences in personality and therefore in reactions to stress situations.

PRYOR, Redwood City, Calif.

A CLINICAL REPORT ON THE TREATMENT OF CONTACT DERMATITIS WITH ADRENOCORTICOTROPIC HORMONE IN OIL. LESLIE N. GAY and GEORGE W. MURGATROYD JR., J. Allergy **23**:215 (May) 1952.

A small group of cases of contact dermatitis is reported. Several were of contact with Rhus toxicodendron. Corticotropin was suspended in peanut oil or sesame oil and injected intramuscularly daily. The dose varied from 25 to 60 mg. The total dose varied up to 300 mg.; the average was 220 mg. Satisfactory results were obtained in each instance.

HOYER, Cincinnati.

TIME OF DAY OF POLLEN SHEDDING OF SOME HAY FEVER PLANTS. MELVIN D. JONES, J. Allergy **23**:247 (May) 1952.

Forty-five species of plants were studied at Lincoln, Neb., in 1945 and at Stillwater, Okla., in 1946 and 1947, to determine the size of pollen and the time of day and time of year of pollen shedding.

Between 90 and 95% of the pollen shed was liberated by most species within a short period of three or four hours each day. The time of day of shedding varied widely for the different species and appeared to be controlled by factors inherent in each species.

The effect of environmental factors on pollen shedding were considered. Temperatures of less than 60 F. inhibited shedding in some species. Wind movement was important in speeding up anthesis, dehiscence, and dispersal. High relative humidity delayed pollen shedding, but did not inhibit it.

HOYER, Cincinnati.

A CLINICAL STUDY OF PHENACETIN-CAFFEINE IN THE TREATMENT OF HAY FEVER. J. RICHARD JOHNSON, JOHN M. SHELDON, KENNETH P. MATHEWS, and ROBERT G. LOVELL, J. Allergy **23**:365 (July) 1952.

Four kinds of tablets were used in a group of 61 patients. One type contained thenylpyramine hydrochloride; another contained this antihistamine and acetophenetidin (Phenacetin) and caffeine. One kind of control tablet was a glucose placebo; another control contained acetophenetidin and caffeine. Each kind of tablet was taken for three consecutive days, four tablets a day. The patients were required to complete forms furnished them, on which they were to record the duration of their symptoms, the severity of their symptoms, the incidence of side-effects, and their opinion of the efficacy of each kind of tablet. The conclusions were that there was essentially no difference among groups of tablets with regard to their effectiveness in relieving hay fever in general and individual symptoms, such as running nose, nasal stuffiness, eye symptoms, sneezing, itching nose and throat, fatigue, and asthma.

HOYER, Cincinnati.

FAMILIAL WHITE SKIN SPOTTING (PIEBALDNESS) ("PARTIAL ALBINISM") WITH WHITE FORELOCK. JEAN V. COOKE, J. Pediat. **41**:1 (July) 1952.

The title describes this very rare congenital disorder. Like piebaldness in horses, it is not related to albinism. In albinism there is inability to form sufficient pigment or to form pigment at all. Here, the trouble is simply one of pigment distribution.

A direct Mendelian trait, not associated with other defects, once lost in an offspring is not likely to appear again.

In contrast to albinism, nevus anemicus, and vitiligo, this is a disorder of the distribution of pigment. It is seen in the forelock, forehead, ventral surfaces of the trunk, and extremities; never in the back. The areas are sharply defined and do not change during growth.

MACDONALD, Pittsburgh.

THE EFFECT OF SODIUM PENTOBARBITAL ON THE TOXICITY OF CERTAIN ANTIHISTAMINES. E. LEONG WAY and WOODROW C. HERBERT, J. Pharmacol. & Exper. Therap. **104**:115 (Feb.) 1952.

Other observers have noted that barbiturates do not lessen the mortality rate in rats poisoned by diphenhydramine (Benadryl) hydrochloride, nor did thiopental (Pentothal) sodium decrease the rate in monkeys given certain antihistamines. The present writers, in similar studies on rats and mice, had similar results but suggested that the degradation products of the antihistamine, which are present in greater amounts after oral administration, may enhance the actions of sodium pentobarbital and contribute to the over-all toxicity.

It is recommended that should the attempt be made in the clinic to antagonize antihistaminic overdosage with a barbiturate, immediate treatment and removal of any unabsorbed material are prime requisites in addition to the usual supportive therapy. PILCHER, Cleveland.

PSYCHOSOMATIC STUDY OF INFANTILE ECZEMA: I. MOTHER-CHILD RELATIONSHIP. MAURICE J. ROSENTHAL, Pediatrics **10**:581 (Nov.) 1952.

Comparison of findings in interviews with the mothers of 25 infants with infantile eczema and of 18 control subjects revealed a significant difference in the infant-rearing practices of these two groups of mothers. Of the mothers in the eczematous group, 60% let their babies cry without picking them up unless the infant had some obvious physical discomfort, whereas this was true of only 16.6% of the mothers in the control group. This finding was taken to indicate that most eczematous infants received inadequate caressing and cuddling. The study did not attempt to evaluate objectively the qualitative character of the skin contact offered the child by the mother.

The lack of cuddling and caressing was felt to be of great, perhaps even of etiologic, prognostic and therapeutic significance, although the data did not rule out the possibility that other factors, such as constitutional predisposition and allergy, were equally important.

The lack of soothing skin contact of the child was found to result most commonly from an attitude on the part of the mother of wishing to be free from being burdened with the care and responsibility of raising a child. These mothers would generally try to justify their infant-rearing practices by saying that they did not wish to "spoil" their babies. In a smaller group of mothers it seemed likely that their relative lack of caressing was due to physical fatigue or weakness. Physicians should attempt to help the mother of an eczematous infant feel more pleased, more at ease, and more adequate in her role as mother.

FROM THE AUTHOR'S SUMMARY.

ERYTHEMA MULTIFORME EXUDATIVUM, WITH A REPORT OF A CASE. GEOFFREY C. DE CRESPIGNY, Clin. Rep. Adelaide Child. Hosp. **2**:86 (Nov.) 1951.

The author presents a case of Stevens-Johnson syndrome which was successfully treated with chlortetracycline (aureomycin). McGUIGAN, Evanston, Ill.

THE CONTENT OF ANTIDIURETIC HORMONE IN THE CEREBROSPINAL FLUID OF INFANTS WITH LEINER'S DISEASE. J. IVADY and G. BUZAS, Ann. paediat. **179**:41 (July) 1952.

An increase of the antidiuretic hormone was found in the cerebrospinal fluid of infants with erythroderma desquamativum which ran parallel with the severity of the illness. Although this increase is not pathognomonic, it occurred in three out of five fatal cases. During the postmortem examination of two infants a duodenal uncus was found. The cerebrospinal fluid produced contractions in the surviving intestine of a guinea pig. It is probable that the inflammatory process is accompanied by an increase of adiuretin.

FROM THE AUTHORS' SUMMARY.

ETIOLOGY OF ACRODYNIA AS THE RESULT OF SENSITIVITY TO MERCURY. E. NAJMAN and C. CETKOVIC, Ann. paediat. **179**:81 (Aug.) 1952.

After applying about 3 to 5 gm. of a 9% mercury ointment, a toxic syndrome was observed in an infant with an exudative dermatitis. There was thrombopenia at first, and after a while acrodynia developed. Idiosyncrasy to mercury is without doubt a frequent cause of acrodynia. On the other hand, the uneven geographic distribution of acrodynia shows that it cannot be the only cause. The authors describe a method for an approximate estimation of mercury in the urine which is clinically very useful. In some cases of hematuria and Henoch-Schoenlein purpura mercury idiosyncrasy seems to play an important part.

FROM THE AUTHORS' SUMMARY.

CLINICAL STUDIES AS TO THE RELATION BETWEEN ALLERGY AND HEPATIC DYSFUNCTION. P. TOLENTINO and S. NORDIO, Minerva pediat. **4**:475 (June 30) 1952.

In the present study, the authors present data to substantiate a thesis many clinicians have expressed that a single noxious agent may produce either allergic manifestations or liver damage, or both. The personal history and blood serum cholinesterase determinations of 49 children with liver dysfunction (18 with icterus, 31 with hepatomegaly) and of 32 children with allergic disorders (asthma, dermatitis, or rheumatic fever) were carefully analyzed. A group of 50 children in the hospital for other disorders served as controls. The data revealed the statistically significant findings that patients with liver disorder were much more likely to have had a previous allergic history and that patients with allergic disorders to have had a previous hepatic dysfunction than were the control children. The serum cholesterase was found to be lower in the children with the hepatic or allergic disorders than in the control children. It would appear that choline substances may constitute the focus of the common noxious agent.

HIGGINS, Boston.

ALLERGY FROM AMBROSIACEA (RAGWEED). F. SABATELLI, Minerva pediat. **4**:587 (July 31) 1952.

Species of the ragweed family found locally about Genoa (Italy) may be responsible for occasional cases of hay fever occurring during July and August.

HIGGINS, Boston.

FAMILIAL OCCURRENCE OF THE EHLERS-DANLOS-SYNDROME: CLINICAL AND PATHOGENETIC CONSIDERATIONS. G. SCHAPER, Ztschr. Kinderh. **70**:504, 1952.

The knowledge about this very rare syndrome (93 cases in the world literature) is enriched by the observations of the author's cases and to the known symptoms of hyperelasticity of the skin, easy vulnerability with tendency toward hemorrhages and hypotonicity of the joints the author adds congenital malformations of the heart and eyes. He considers the syndrome a constitutional mesenchymal dystrophy which is inherited as a dominant characteristic.

GLASER, Jerusalem.

ECTODERMOSIS EROSIVA PLURIORIFICIALIS. L. VAN DEN BULCKE and N. HAVERJAMP BEGEMANN, Maandschr. kindergeneesk. **20**:340 (Nov.) 1952.

The authors report a case of erythema multiforme, pluriorificial form, treated with chlortetracycline (aureomycin). Cold agglutinins were found in the serum. There was bronchitis, but the x-rays showed no infiltrations in the lungs.

FROM THE AUTHORS' SUMMARY.

Surgery and Orthopedics

TREATMENT OF SURGICAL SHOCK. ARKELL M. VAUGHN, Illinois M. J. **102**:297 (Nov.) 1952.

The surgeon must always try to prevent shock. It it does occur, he may use empiric treatment, which includes rest, warmth, elevation of feet, tight bandaging of the extremities, use of sedatives, stimulants and vasospastics, and specific treatment, which consists mainly of liberal blood transfusions supplemented by plasma, oxygen, the crystalloids, and drugs.

BARBOUR, Peoria, Ill.

Teeth and Dentistry

ADVANCES IN PEDIATRIC SURGERY. VICTOR RICHARDS, California Med. **77**:293 (Nov.) 1952.

Recent advances in pediatric surgery have been made in several fields. Hydrocephalus is again being treated by draining the cerebrospinal fluid into the ureter, the mastoid antrum, or the peritoneal cavity. Funnel chest should be corrected surgically. Congenital atresia of the esophagus is best treated by a one-stage operative repair. Patent ductus should be closed. Operations are available for cyanotic children. Intussusception is again being treated by barium enema in selected cases. Megacolon can be benefited by surgical procedures, which now are directed at the distal spastic segment rather than the proximal dilated segment.

PRYOR, Redwood City, Calif.

Miscellaneous

THE PHYSIOLOGICAL BASIS OF SHOCK. HARRY H. LEVEEN, Illinois M. J. **102**:362 (Dec.) 1952.

LeVeen points out that trauma, whatever its nature, results in a negative nitrogen balance. The liberation of adrenocorticotropin hormone by the pituitary gland is responsible for the toxic loss of nitrogen. Cortisone causes this negative nitrogen balance by transforming body protein into sugar. The end-results of this transformation are a diminution of body protein stores, an increase in the carbohydrate stores, and the formation and excretion of urea. This is known to be a beneficial reaction, not a sustaining one.

Impairment of liver function accounts for the sustaining mechanism in shock; a lactic acidemia occurs with a resulting reduction in carbon dioxide-combining power. The oxygen saturation of the portal vein drops to 20% in early shock. The portal vein is the source of 75% of the liver's supply of oxygen. The output of the hepatic artery is also thus reduced. All these factors make possible a high degree of liver anoxia early in shock and of greater extent than the anoxia found in other tissues.

The mystery of the peripheral circulatory failure in shock has been solved by the demonstration of a circulating vasodepressor material. This material, produced by ischemic muscle and liver tissue, in turn produces a paralysis of the precapillary sphincters, with the result that they no longer respond to nerve impulses or epinephrine. The net result is a fall in venous pressure, a decreased cardiac output, and a drop in blood pressure. The vasodepressor material is not metabolized by the ischemic liver and accumulates in shock.

Liver ischemia explains quite well the biochemical and peripheral vascular phenomena in most of the types of shock. Other tissues are injured by the hypoxia which accompanies shock. The tissue anoxia damages all tissues, but in no tissue is the need for oxygen more vital than it is in the liver.

If part of the normal pituitary-adrenocortical defense mechanism is nonfunctional, shock may result from a mild stress. In the newborn, the pituitary may not respond to stress for two weeks. The use of corticotropin (ACTH) would then be desirable.

BARBOUR, Peoria, Ill.

HYGROMA COLLI: A RETROPHARYNGEAL TUMOR SIMULATING AN ANGIOMATOUS GROWTH. H. E. STADLER, J. K. BERMAN, and T. W. JOHNSON, J. Pediat. **41**:100 (July) 1952.

The authors report a cystic hygroma of the neck which was multiloculated. The hygroma in the neck and the secondary cysts contained blood. In the retropharynx, the cyst interfered with respiration and deglutition. Extensions of the cyst involved the superior mediastinum, the

pleura, the aortic arch, the internal jugular vein, the carotid artery, and the vagus nerve. The patient was a boy aged 1 year. The treatment consisted of radical surgical excision. The patient recovered.

MACDONALD, Pittsburgh.

DIPHENHYDRAMINE HYDROCHLORIDE U.S.P. XIV AND RESPIRATORY TRACT FLUID. SHIRLEY M. R. BIDWELL and ELDON M. BOYD, J. Pharmacol. & Exper. Therap. **104**:224 (Feb.) 1952.

As several expectorant cough mixtures containing an antihistaminic drug were made commercially available to physicians in 1950 and 1951, this study was made to learn whether diphenhydramine hydrochloride had any expectorant properties. The answer was in the negative. The study was continued during a full year to avoid possible seasonal variations in the results. "It would seem that the consistent conclusions obtained in such divergent species as rabbits, cats, guinea pigs and albino rats, could be extrapolated to man with reasonable certainty. These results suggest, therefore, that the inclusion of diphenhydramine hydrochloride, and perhaps other antihistaminic drugs, in expectorant cough mixtures contribute little if any to the reputed effect of such cough mixtures upon the rate of output of respiratory tract fluid in man. One should look elsewhere in attempting to explain the value of adding antihistaminic drugs as adjuvants to expectorant cough mixtures."

PILCHER, Cleveland.

News and Comment

ANNOUNCEMENT

American Academy for Cerebral Palsy.—The 7th annual meeting of the American Acamedy for Cerebral Palsy will be held on Oct. 30-31, 1953, in Fort Worth, Texas, at the Western Hills Hotel.

CORRECTION

In the Transactions of the American Pediatric Society, published in the September, 1953, issue, page 327, the name of the second author of "Some Effects of Thyroid or Thyroxin upon Premature Infants" is Dr. T. S. Danowski.

Directory of Pediatric Societies *

INTERNATIONAL

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 16 rue du Mont Blanc, Geneva, Switzerland

IV° Congreso Pan-Americano de Pediatria

President: Dr. Leonel Gonzaga.
General Secretary: Dr. Adamastor Barbosa.
Secretariat: Rua Dias da Rocha 25, ap. 602, Copacabana, Rio de Janeiro.
Place. Rio de Janeiro. Time: 1954.

IV° Congreso Sudamericano de Pediatria, Confederacion Sudamericano de Sociedades de Pediatria

President: Prof. Carlos Prado.
Vice-President: Dr. Marcelo Garcia.
General Secretary: Dr. Alvaro Aguiar.
Place: Avenida Mem de Sá 197, Rio de Janeiro. Time: 1954.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. Bernard Laski, Toronto.
Secretary: Dr. Crawford Anglin, Toronto.
Place: Academy of Medicine.

Asociación de Pediatras Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marin and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Australian Paediatric Association

President: Dr. P. A. Farnshaw, Ballow Chambers, Wickham Terrace, Brisbane. B17.
Honorary Secretary-Treasurer: Dr. D. C. Jackson, 217 Wickham Terrace, Brisbane. B17.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Prof. J. Smellie.
Secretary: Prof. Alan Moncrieff, Institute of Child Health, The Hospital for Sick Children, Great Ormond St., W. C. 1, London.
Place: Windermere. Time: Between Easter and Whitsunday.

Canadian Paediatric Society

President: Dr. D. B. Leitch, 210 McLeod Bldg., Edmonton, Al.
Secretary: Dr. R. L. Denton, 1615 Cedar Ave., Montreal 25.

Danish Pediatric Society

President: Dr. A. Rothe-Meyer, Children's Hospital Fûglebakken, Copenhagen F.
Secretary: Dr. E. Winge Flensborg, Children's Hospital, Martinsvej, Copenhagen V.
Place: Different hospitals. Time: First Wednesday of every month.

Departmento de Pediatria da Associação Paulista de Medicina

President: Dr. Oswaldo Riedel de Souza e Silva.
Secretaries: Dr. Ovidio Collesi.
Dr. Helda Elina Vieira de Barros.
Place: Avenida Brigadeiro Luiz Antonio, 278, São Paulo, Brasil.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. Dr. med. B. de Rudder, Frankfort/Main, Universitats-Kinderklinik.
Secretary: Prof. Dr. med. Jochims, Stadtische Kinderklinik, Lubeck.

Hellenic Society of Pediatrics

President: Dr. Spiros Charocopos, Alexandras Ave. 1, Athens.
Secretary: Dr. Nikas Zervos.
Place: Amphitheater, Medical School of the University of Athens. Time: Once a month.

Nederlandse Vereeniging voor Kindergeneeskunde

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. Arne Njå, Sporveisgt. 29, Oslo.
Secretary: Dr. Helge Granrud, Abbedikollen 38, Bestun, Oslo.
Place: Barneklinikken, Rikshospitalet, Oslo. Time: Friday, six times a year.

Pediatric Society of New Zealand

President: Dr. Edward J. Cronin, Power Board Bldg., Queen St., Auckland.
Secretary: Dr. J. D. Matthews, 104 Symonds St., Auckland.

Philippine Pediatric Society

President: Dr. Renato Ma. Guerrero.
Secretary: Dr. Felix A. Estrada.
Place: Santo Tomas University Hospital and other pediatric centers. Time: Every two months.

Royal Society of Medicine, Section of Paediatrics

President: Dr. D. W. Winnicott.
Secretary: Dr. J. J. Kempton; Dr. A. P. Norman.
Sectional Editor: Dr. D. MacCarthy
Place: 1 Wimpole St., London W.1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: P. D. Dr. F. Bamatter, St.-Léger 8, Genève.
Secretary: Dr. M. Nicod, Place Bel-Air 2, Lausanne.

Sociedad Argentinade Pediatrie

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

Sociedad Boliviano de Pediatria

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedade Brasiliera de Pediatria

For officers, see IV° Congreso Sudamericano de Pediatria, above.

Sociedad Chihuahuense de Pediatría

President: Dr. Alfonso Ruiz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

Sociedad Chilena de Pediatria

President: Prof. Dr. Raúl Gantes A.
Secretary General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

Sociedad Colombiana de Pediatria

President: Dr. Jorge Camacho Gamba.
Vice-President: Dr. Antonio Alvarez Riaño.
Secretary: Dr. Hernando Vanegas A.
Treasurer: Dr. Efrain Perry Villate.

Sociedad Cubana De Pediatria

President: Prof. Agustin Castellanos y Gonzales.
Secretary: Dr. Carlos Hernandez Miyares, Apartado 2430, Habana.
Place: Catedra de Clinica Infantil Hospital Nuestra Senora de las Mercedes and Hospital Municipal de Infancia, Habana. Time: 9 p.m., last Wednesday of every month.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Próspero Arriagada.
Secretary: Dr. Guillermo Repetto D.
Place: Hospital Clinico Reginal Concepción. Time: 7:30 p.m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatria del Litord

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary General: Dr. Elsa Galimany.

Sociedad de Pediatria y Puericultura del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Teasurer: Dr. Hernando Borrios Angulo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Vice-President: Dr. Breno Barcellos.
Secretary: Dr. Enio Pilla and Dr. Damasceno Tilho.
Treasurer: Dr. J. Sant' Ana Aúde.

Sociedade Portugesa de Pediatria

President: Prof. Dr. Lucio de Almeida.
Vice-President: Dr. Cordeiro Ferreira.
Secretary General: Prof. Dr. Carlos Salazar de Sousa.
Treasurer: Dr. Mario Cordeiro.
Place: Clinica pediatrica do Hospital D. Estefania, Lisbon. Time: Monthly.

Sociedad Uruguaya de Pediatria

President: Dr. Euclides Peluffo.
Secretary: Dr. Ruben Gorlero Bacigalupi.
Place: Av. Agraciada 1464, piso 13, Montevideo.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. Guillermo Rangel.
Secretary: Dr. Guillermo Tovar E., P.O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. Humberto Perez Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

LA SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Henri Charbonneau, 3095 Sherbrooke, Montréal.
Secretary: Dr. Edmond Baril, 301 Carré St-Louis, Apt. 1, Montréal.
Time: Second Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Prof. Jean Cathala, 45 rue Scheffer, Paris XVI.
Secretary: Prof. Maurice Lamy, 94 rue de Varenne, Paris VII.
Place: Hôpital des Enfants Malades, 149 rue de Sèvres, Paris XV. Time: 4 p.m., third Tuesday of each month.

SOCIÉTÉ DE PÉDIATRIE DE QUÉBEC

President: Dr. Roland Thibaudeau, 203 des Erables, Québec.
Secretary: Dr. Euclide Dechêne, 312 du Roi, Québec.
Place: Quebec. Time: May and November.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Seymour Heymann, 804 Medical Centre, Jeppe St. Johannesburg.
Honorary Secretary-Treasurer: Dr. I. Kessel, Transvaal Memorial Hospital for Children, Milner Park, Johannesburg.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. Karl-Axel Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent Urban Hjarne, Stockholm.
Secretary: Dr. M. d'Avignon, Pediatric Clinic, Karolinska Sjukhuset, Stockholm 60.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm, and Pediatric Clinic, Uppsala. Time: Second Friday of each month, except summer.

UNITED STATES

National

AMERICAN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. Wyman C. C. Cole, 3001 W. Grand Blvd., Detroit.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Warren W. Quillian, 140 Alhambra Circle, Coral Gables, Miami 34, Fla.
Secretary: Dr. E. H. Christopherson, 636 Church St., Evanston, Ill.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Robert Ward.
Vice-President: Dr. Russell Blattner, Houston, Texas.
Secretary-Treasurer: Dr. Sydney S. Gellis, Boston.

THE AMERICAN PEDIATRIC SOCIETY

President: Dr. Rustin McIntosh.
Vice-President: Dr. Wilburt C. Davison.
Secretary-Treasurer: Dr. Aims C. McGuinness.

Sectional

Intermountain Pediatric Society

President: Dr. John T. Mason.
Secretary: Dr. Stanley R. Child.
Place: Ambassador Athletic Club, Salt Lake City. Time: 7 p.m.

New England Pediatric Society

President: Dr. Albert W. Fellows.
Secretary: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston, except Spring meeting. Time: Wednesdays, four times a year.

North Pacific Pediatric Society

President: Dr. Carl Ashley, 2455 N. W. Marshall St., Portland, Ore.
Secretary-Treasurer: Dr. S. Gorham Babson, 1107 S. W. 13th St., Portland, Ore.

Northwestern Pediatric Society

President: Dr. F. G. Hedenstrom, 420 Lowry Medical Arts Bldg., St. Paul.
Secretary: Dr. Charles L. Steinberg, 1118 Lowry Medical Arts Bldg., St. Paul.
Place: Minneapolis; St. Paul; Duluth, Minn., and Rochester, Minn. Time: January, April, July, and October.

Rocky Mountain Pediatric Society

President: Dr. John Lichty, Pediatric Department, Colorado General Hospital, 4200 E. 9th Ave., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Announced by mail. Time: Monthly dinner meetings, October to June.

Southwestern Pediatric Society

President: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Carl A. Erickson, 960 E. Green St., Pasadena, Calif.
Place: Jonathan Club of Los Angeles. Time: 6:30 p.m., second Wednesday in January, March, May, September, and November.

State

Alabama Pediatric Society

President: Dr. David B. Monsky, 748 Adams St., Montgomery 5.
Secretary: Dr. Alice H. Pye, 305 Church St., Montgomery.
Place: Montgomery.

Arizona Pediatric Society

President: Dr. Henry E. Running.
Secretary: Dr. William F. Schaffman.
Time: On Call.

California Medical Association, Section on Pediatrics

Chairman: Dr. Joseph W. St. Geme, 511 S. Bonnie Brae, Los Angeles 5.
Secretary: Dr. Alvin H. Jacobs, 2201 Webster St., San Francisco 15.
Assistant Secretary: Dr. Clement J. Molony, 416 N. Bedford Dr., Beverly Hills.

Florida State Pediatric Society

President: Dr. Charlotte C. Maguire, 1413 Kuhl Ave., Maguire Bldg., Orlando.
Secretary-Treasurer: Dr. Wesley S. Nock, 273 Alhambra Circle, Coral Gables.

Georgia Pediatric Society

President: Dr. John A. Simpson Athens.
Secretary: Dr. J. Harry Lange, 490 Peachtree St., Atlanta.
Place: Savannah. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Joseph Hetzel, 51 Central Ave., Waterbury.
Secretary: Dr. James H. Root Jr., 103 N. Main St., Waterbury.
Time: With the Connecticut State Medical Society in the spring, with the Connecticut State Clinical Congress in the fall; winter meeting usually in December.

Illinois State Medical Society, Section on Pediatrics

Chairman: Howard R. Miller, 418 Jefferson Bldg., Peoria 2.
Secretary: Harry H. Boyle, 2376 E. 71st St., Chicago 49.

Indiana State Pediatric Society

President: Dr. Harold D. Lynch, Evansville.
Secretary: Dr. L. T. Meiks, Indianapolis.

Iowa Pediatric Society

President: Dr. Charles J. Baker, 403 Carver Bldg., Fort Dodge.
Vice-President: Dr. P. E. Gibson, Davenport Pediatric Group, Davenport.
Secretary-Treasurer: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting. Fall meeting at University Hospital, Iowa City.

Massachusetts Hospital Association

President: Dr. Philip D. Bonnet, Administrator, Massachusetts Memorial Hospitals, Boston.
Executive Secretary: Henry G. Brickman, 14 Somerset St., Boston 8.

Michigan State Medical Society, Pediatric Section

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary: Dr. Park S. Bradshaw, 1014 Jefferson St., Muskegon.

Montana Pediatric Society

President: Dr. Orville M. Moore, 555 Fuller Ave., Helena.
Secretary: Dr. Joseph W. Brinkley, 410 Central Ave., Great Falls.
Place: Variable. Time: Spring and fall.

Nebraska Pediatric Society

President: Dr. Michael Crofoot.
Vice-President: Dr. Donald C. Nilsson.
Secretary-Treasurer: Dr. A. J. Lombardo, 401 Aquila Ct., Omaha.
Place: Children's Memorial Hospital. Time: 6 p.m., dinner, third Thursday of each month.

New Hampshire Pediatric Society

President: Dr. Douglass W. Walker, Laconia.
Secretary: Dr. Wm. D. Penhale, Concord.
Place. Alternately Concord, Hanover, Laconia, and Manchester. Time: Four times a year.

New Mexico Pediatric Society

President: Dr. M. K. Wylder, Suite 14, Medical Arts Sq., Albuquerque.
Secretary: Dr. Ly Werner, Suite 25, Medical Arts Sq., Albuquerque.
Place: Variable. Time: Every two or three months.

North Carolina Pediatric Society

President: Dr. Eugene Keiter, Kinston Clinic, Kinston.
Vice-President: Dr. Donald Robinson, 308 W. Davis St., Burlington.
Secretary-Treasurer: Dr. Robert Pope, Wilson Clinic, Wilson.
Place: Roaring Gap and Chapel Hill. Time: Sept. 12 and Oct. 30, respectively.

South Carolina Pediatric Society

President: Dr. Walter Moore Hart, 117 W. Cheves St., Florence.
Secretary: Dr. John R. Paul Jr., 82 Rutledge Ave., Charleston.
Place: Columbia, S. C. Time: Second Monday and Tuesday in September.

Tennessee Pediatric Society

President: Dr. O. L. Von Canon, 846 McCallie Ave., Chattanooga.
Secretary: Dr. Oliver W. Hill, 4807 Newcom Ave., Knoxville.

Texas Pediatric Society

President: J. A. Bybee, Beaumont.
President-Elect: Dr. Robert L. Moore, Dallas.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco.
Treasurer: Dr. Jack M. Woodall, Big Springs.

Virginia Pediatric Society

President: Dr. Edwin L. Kendig Jr.
Secretary: Dr. T. J. Humphries.

Wisconsin State Medical Society

Chairman: Dr. N. L. Low, Racine
Vice-Chairman: Dr. E. H. Pawsat, Fond du Lac.
Secretary: Dr. Samuel E. Kohn, Milwaukee.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave., Cleveland 12.
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p.m., October, December. February, and March.

Baltimore City Medical Society, Pediatric Section

President: Dr. Wilson Grubb, 4 E. 33d St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.
Place: 1211 Cathedral St., Baltimore 1. Time: 8:30 p.m., second Tuesday in November, January, and March.

Bronx Pediatric Society

President: Dr. M. H. Grand, 1749 Grand Concourse, New York.
Secretary: Dr. Charles T. Fried, 1220 Grand Concourse, New York.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August, and September.

Brooklyn Academy of Pediatrics

President: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn.
Secretary: Dr. Henry Cohen, 1761 E. 19th St., Brooklyn.
Place: Granada Hotel, Brooklyn. Time: 8:45 p.m., fourth Wednesday of February, March, April, October, and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold.
Secretary: Dr. Richard A. Downey.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p.m., first Monday of each month, September to June.

Central New York Pediatric Club

President: Dr. Frank Williams, 58 Swan St. S., Albany.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester.
Place: Various cities in New York State; fall meeting jointly with Upper New York State Academy of Pediatrics. Time: Third Tuesday of April and October.

Central Ohio Pediatric Society

President: Dr. O. W. Hosterman, 350 East Broad St., Columbus 15.
Secretary-Treasurer: Dr. John Riepenhoff, 2998 Sullivant Ave., Columbus.
Place: As announced. Time: Third Wednesday of September, November, January, March, and May.

Chicago Pediatric Society

President: Dr. Alfred S. Traisman.
Vice-President: Dr. Eugene T. McEnery.
Secretary: Dr. Matthew M. Steiner, 6354 N. Broadway.
Treasurer: Dr. Maxwell P. Borovsky.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Clare R. Rittershoffer, 301 Erkenbrecker.
Secretary: Dr. Joseph E. Ghory, 5 Stevenson Ln.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. Edwin A. Danford.
Secretary: Dr. Jack F. McKemie.
Place: As announced. Time: 7:30 p. m., fourth Wednesday of January, March, May, July, September, and November.

Dade County Pediatric Society

President: Dr. Lynn Whelchel, DuPont Bldg., Miami, Fla.
Secretary: Dr. Howard Engle, 311 Lincoln Rd., Miami Beach, Fla.

Dallas Pediatric Society

President: Dr. Floyd A. Norman, 4325 Cole Ave., Dallas.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.
Place: Children's Hospital of Texas. Time: 6:30 p. m., first Thursday in each month.

Detroit Pediatric Society

President: Dr. Ruben Meyer, 938 Maccabees Bldg., Detroit.
Secretary: Dr. W. W. Zuelzer, Children's Hospital of Michigan, Detroit.
Place: Variable. Time: Five times a year.

Honolulu County Pediatric Society

President: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.
Corresponding Secretary and Treasurer: Dr. John H. Peyton, Kauikeolani Children's Hospital, Honolulu.

Honolulu Pediatric Society

President: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu.
Recording Secretary: Dr. M. H. Hasegawa.
Corresponding Secretary: Dr. John Peyton, Kauikeolani Children's Hospital, Honolulu.
Place: At doctors' homes in rotation. Time: 6 p.m., third Thursday of each month.

Houston Pediatric Society

President: Dr. Emanuel B. Brandes, 3101 Fannin St., Houston.
Secretary: Dr. Robert D. Lomas, 5101 Fannin St., Houston.
Place: River Oaks Country Club. Time: 7:30 p.m., fourth Tuesday of each month.

Kansas City Southwest Pediatric Society

President: Dr. Frank Hogue, Plaza Medical Bldg., Kansas City, Mo.
Secretary: Dr. S. J. Kranson, Truman Rd. and Ash, Independence, Mo.
Place: University Club, Kansas City, Mo. Time: On call.

Long Beach Pediatric Society

President: Dr. Kenneth Berkaw, 211 Cherry Ave., Long Beach, Calif.
Secretary: Dr. C. W. Latshaw, 3821 Atlantic Ave., Long Beach, Calif.
Place: Victor Hugo Restaurant, 730 E. Broadway. Time: First Tuesday night of every month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.
Secretary: Dr. Arthur J. Holmes, 65 N. Madison Ave., Pasadena 1.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd., Los Angeles Time: Second Thursday of alternate months beginning in September.

Louisville Pediatric Society

President: Dr. Lee Palmer.
Secretary: Dr. Martin Z. Kaplan.
Place: Variable. Time: Five times a year.

Medical Society of the County of Kings and Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Max Palinsky, 1270 45th St., Brooklyn 19.
Secretary: Dr. Bernard Greenberg, 670 Ocean Ave., Brooklyn 26.
Place: Kings County Medical Society Auditorium, 1313 Bedford Ave., Brooklyn. Time: 9 p.m., fourth Monday of January, March, April, October, and November.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington 20.
Secretary: Dr. John E. Cassidy, 5402 Connecticut Ave. N.W., Washington.
Place: Medical Society Bldg., 1718 M St. N.W., Washington. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. James G. Hughes, 20 S. Dunlap, Memphis.
Secretary: Dr. George S. Lovejoy, 609 N. Highland, Memphis.
Place: Rotated among four hospitals. Time: 7:30 p.m., second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. Franklin Mellencamp, 1513 E. Capitol Dr., Milwaukee.
Secretary: Dr. Karl Beck, 1411 Wauwatosa Ave., Milwaukee.
Place: Milwaukee University Club. Time: Second Wednesday of February, April, June, and October.

Mobile Pediatric Society

President: Dr. Daniel Sullivan, 1420 Government St., Mobile, Ala.
Secretary: Dr. Robert O. Harris III, 1514 Government St., Mobile, Ala.
Place: Admiral Semmes Hotel. Time: 7:30 p.m., fourth Thursday of September, November, January, March, and May.

Nashville Pediatric Society

President: Dr. Thomas Weaver, Bennie Dillon Bldg., Nashville, Tenn.
Secretary: Dr. Ethel Walker, 3415 West End Ave., Nashville, Tenn.
Place: Homes of members. Time: Third Thursday of every month.

Nassau Pediatric Society

President: Dr. Daniel Blitz, 1 Club Drive, Woodmere, N. Y.
Secretary-Treasurer: Dr. David J. Posner, 98 Wolcott Rd., Levittown, N. Y.
Place: Garden City Hotel, Garden City, L. I., N. Y. Time: 7:30 p. m., second Monday of October, December, February, April, and June.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Jerome L. Kohn, 50 W. 96th St., New York 25.
Secretary: Dr. Lawrence B. Slobody, 1 E. 105th St., New York 12.
Place: New York Academy of Medicine, 2 E. 103d St. Time: 8:30 p.m., second Thursday of each month, November to May, inclusive.

Northern California Pediatric Society

President: Dr. John A. Anderson, Stanford Hospital, 2351 Clay St., San Francisco 15.
Secretary: Dr. Edward Campion, 1018 E St., San Rafael.
Place: San Francisco. Time: Quarterly, as speakers are available.

Oklahoma City Pediatric Society

President: Dr. C. M. Bielstein, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Louis Frank, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. John B. Bartram, 2600 Lawrence St., Philadelphia 33.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p.m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Christian John Stoecklein, 519 Medical Arts Bldg., Pittsburgh 13.
Secretary-Treasurer: Dr. James W. Stirling, 694 Lincoln Ave., Pittsburgh 2.
Place: Western State Psychiatric Institute and Clinic. Time: Second Friday in October, December, February, and April.

Queens Pediatric Society

President: Dr. Samuel Dillon, 119-20 Rockaway Beach Blvd., Rockaway Park, N. Y.
Secretary: Dr. Moe Goldstein, 111-32 76th Ave., Forest Hills, N. Y.
Place: Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

Richmond Pediatric Society

President: Dr. Hobart T. Dougan, 1832 Monument Ave., Richmond 20, Va.
Secretary: Dr. Robert A. Hoffman, 1001 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p.m., third Thursday of each month, except June, July, and August.

San Antonio Pediatric Society

President: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Secretary: Dr. Virginia S. Stovall, 1116 S. Texas Bldg., San Antonio 5.
Time: 7:30 p. m., supper, first Tuesday of each month.

Seattle Pediatric Society

President: Dr. O. William Anderson.
President-Elect: Dr. Robert Tidwell.
Secretary-Treasurer: Dr. James L. Tucker.
Place: College Club. Time: 6:30 p.m., fourth Friday of each month from September to June.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway.
Secretary: Dr. John C. Herweg.
Place: Candlelight House, 7800 Clayton Rd. Time: 6:30 p.m., second Thursday of each month from October to May, inclusive.

Santa Barbara Pediatric Society

President: Dr. Clarence B. Hills, 22B. W. Micheltorena St., Santa Barbara, Calif.
Secretary: Dr. Louise P. Brown, 3017 Foothill Rd., Santa Barbara, Calif.
Place: Varies. Time: Two to three times yearly, on call.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Fred J. Chapin, 101 John St., Bay City.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Ann Arbor.
Place: University Hospital, Ann Arbor.

Waco Pediatric Society

President: Dr. J. M. Garrett, 1408 Austin Ave., Waco, Texas.
Secretary: Dr. C. G. Shellenberger, 1318 Austin Ave., Waco, Texas.
Place: 1917 Austin Ave., Waco, Texas. Time: Third Tuesday of each month.

Westchester County Medical Society, Pediatric Section

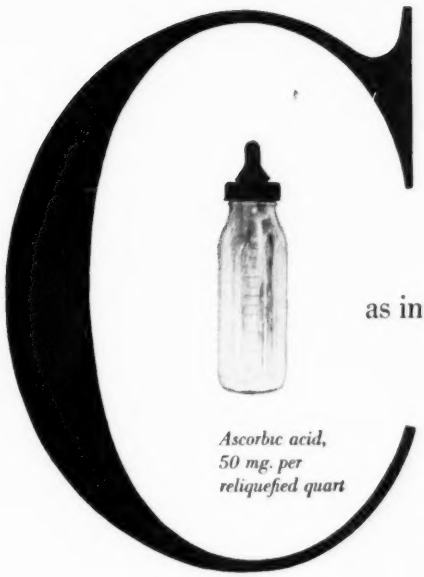
President: Dr. Herbert Kahan, 650 Main St., New Rochelle, N. Y.
Secretary: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Four dinner meetings a year, November, February, April, and June.

Western Michigan Pediatric Society

President: Dr. A. Morgan Hill, 310 Fulton, E., Grand Rapids.
Secretary: Dr. John C. Montgomery, 1810 Wealthy St., S.E., Grand Rapids.
Place: Two meetings in Grand Rapids, two elsewhere. Time: First Wednesday of October November, April, and May.

Wichita Pediatric Society

President: Dr. Frank L. Menehan.
Secretary: Dr. R. C. Knappenberger.
Place: Homes of members. Time: 8:30 p. m., first Thursday, October through May.



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and
correct

as in **SIMILAC**

Ascorbic acid, 50 mg. per reliquefied quart

Similac provides, constantly and unvaryingly, 50 mg. of ascorbic acid per reliquefied quart—an amount closely approximating the content of mother's milk—and in excess of recommended allowances. Similac thus assures adequate and continuous (through each feeding) Vitamin C intake now established as an effective safeguard against scorbutic and some anemic states during infancy.[1] The importance of an adequate intake is further reflected in the finding that Vitamin C is essential for utilization of the amino acid tyrosine, functioning probably as coenzyme.[2]

There is no closer equivalent to the milk of healthy, well-nourished mothers than Similac

providing: zero curd tension for easy digestion; fats chosen for maximum retention and high ratio of unsaturated and essential fatty acids; full balanced array of essential amino acids; folic acid and Vitamin B_{12} (naturally occurring, in breast milk quantities); other vitamins in adequate amounts; minerals adjusted to favorable proportions.

Supplied: Similac Powder, tins of 1 lb.; Similac Liquid, tins of 13 fl. oz.

1. Tisdall, F. F., and Jolliffe, N., in Clinical Nutrition, New York, P. B. Hoeber, 1950, c. 23, p. 590. 2. Seabock, R. R., and Goodland, R. L.: Science *114*: 645 (Dec. 14) 1951.

A QUARTER CENTURY OF PROGRESS IN INFANT NUTRITION
M&R NUTRITION RESEARCH SERVICE

M & R Laboratories • *Columbus 16, Ohio*

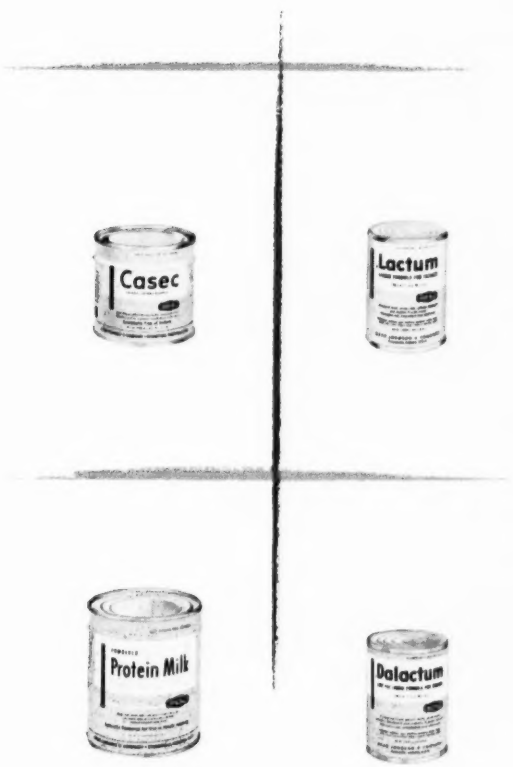
why

Why Does Mead Johnson & Co.

M E A D J O H N S O N

13?

Manufacture 13 Different Infant Formula Products?



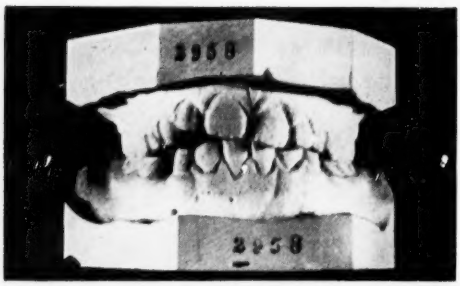
In the important field of infant nutrition, for nearly half a century, Mead Johnson & Company has endeavored to provide physicians with a group of formula products designed to meet every possible individual nutritional requirement of babies that might be encountered in daily practice.

This means not only the manufacture of basic formula products for normal healthy infants but also the development of products to help solve the wide variety of difficult feeding problems that constantly occur. Such a goal can be achieved only through wide experience and through diversification of research projects to encompass the full scope of infant nutrition.

That is why today we manufacture 13 infant formula products, many times the number produced by any other company. Several of these 13 are products with very limited applications and are actually manufactured at a loss because of our determination to assure optimum service to the medical profession at a reasonable cost to patients.

This is a fundamental phase of the policy to which Mead Johnson & Company is dedicated — that of serving the medical profession. This is and always will be the most important product of our Company.

& COMPANY MEAD



Nine year old boy had habit of holding index finger between teeth. Pressure caused teeth to protrude so that they do not meet.

Hand of above patient shows deformity caused by biting on finger. Note callous over joint and rotated tip of finger.

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OF PERSISTENT FINGER-SUCKING

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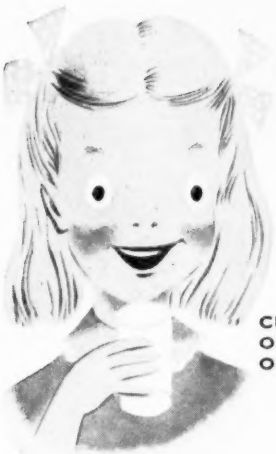

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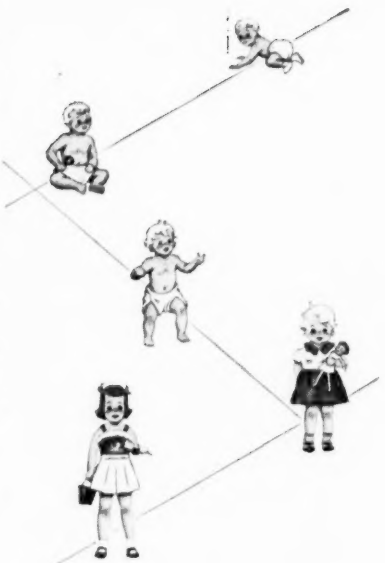

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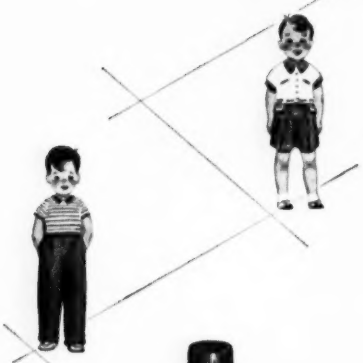

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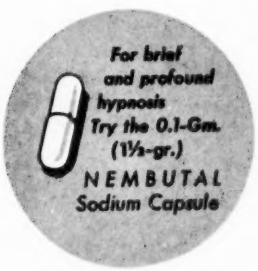

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